Transfusion Medicine - Historical Background and the Legislation

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SUMMARY

Introduction: More than 300 years have passed from the first attempts to use blood for therapeutic purposes, to scientifically based postulates of blood use. Each generation of physicians, faced with the need for clinical transfusions to save lives, has contributed to the safety and acceptance of transfusions by tackling the lack of laboratory equipment, legislation and even adequately trained medical staff. To indicate the existing regulations for a significant clinical area of Clinical transfusion medicine as a separate entity.

Material and Methods: Online search of the historical and medical development of transfusion and international and domestic regulations in the field of transfusion medicine. A literature search was conducted using PubMed, Cochrane, Embase, and Scopus databases. The search was done on the following keywords: transfusion medicine, regulative, doctor’s education, history of transfusion.

Topic: The first successful human-to-human transfusion directly from vein to vein was performed in 1818 by the English physician Dr. James Blundell. As blood groups were not known at the time, this transfusion was successful by chance. In 1901, the Austrian doctor Dr. Karl Landsteiner discovered the ABO blood group system, so the transfusion became safer.

Over the decades, the blood establishment has been improved both organizationally and functionally in order to ensure the safest possible blood. Blood banks in 1970’s move toward an all-volunteer blood donor system. The turning point for the organization of hospital blood banks was 1987, when the European directive provided for the gathering of member states on the legal responsibility for blood products, starting in July 1988.


So far, 8 editions of the guidelines „Red Book” have been published. Based on international guides and standards, it can be said that the clinical transfusion of the Republic of Serbia has developed in parallel with world trends.

The European Commission operates through recommendations (EC recommendations), of which the most important in practice are: Recommendation No.R (88) 4 concerning the responsibility of health authorities in the field of blood transfusion.

Modern therapeutic procedures include vigilance system which is why it was formed European Haemovigilance Network (EHN) in 1998, from which the International Haemovigilance Network was formed later in 2009 (IHN).
**INTRODUCTION**

Blood transfusion is the process of donating blood or blood components from a donor to a recipient of blood or blood components [1,2].

More than 300 years have passed from the first attempts to use blood for therapeutic purposes, to scientifically based postulates of blood use. Each generation of physicians, faced with the need for clinical transfusions to save lives, has contributed to the safety and acceptance of transfusions by tackling the lack of laboratory equipment, legislation and even adequately trained medical staff [3,4,5].

To give a historical overview of transfusion medicine and indicate the previous and existing regulations and legislation for a significant clinical area of Clinical Transfusion Medicine as a separate entity.

**MATERIAL AND METHODS**

Online search of the historical and medical development of transfusion and international and domestic regulations in the field of transfusion medicine. A literature search was conducted using PubMed, Cochrane, Embase, and Scopus databases. The search was done on the following keywords: *transfusion medicine*, *regulative*, *doctor’s education*, *history of transfusion*.

**TOPIC**

In the development of transfusion medicine, it is important to mention the events in clinical practice and the emergence of regulations that paved the way for the development of clinical transfusion medicine. Clinical transfusion medicine, although a young branch of medicine, with knowledge that has been implied for centuries, has only in the last fifty years had precise medical legislation and professional methodological doctrine [6].

**Early development before blood group discovery**

From 1616 to the present day, the following medical and historical moments were crucial: In 1616, Dr. William Harvey, a physician from England, determined that blood circulates through the body as a systemic circulation, assuming that the heart pumps one part of the circulation around the brain and the other through the body. Further research by Dr. William Harvey in 1628 established that it was a single blood circulation [4,7].

As in all other medical procedures, the clinical implementation was preceded by an experimental phase, so in 1665 Dr. Richard Lower performed the first successful blood transfusion from dog to dog [8]. An attempt to perform an animal-to-human transfusion resulted in numerous deaths, which is why in 1678 the Pope banned the transfusion [5,6,9].

The first successful human-to-human transfusion directly from vein to vein was performed in 1818 by the English physician Dr. James Blundell. As blood groups were not known at the time, this transfusion was successful by chance. Poor outcomes in majority of cases led to the ban on transfusion as a medical procedure [5,10,11].

**Further development after blood group discovery**

In 1901, the Austrian doctor Dr. Karl Landsteiner discovered the blood groups of the ABO system, so the transfusion became safer. Dr. Karl Landsteiner received the Nobel Prize in 1930 for this discovery [3,5,9,10,12].

In 1907 Hektoen suggested that the safety of transfusion might be improved by crossmatching blood between donors and patients to exclude incompatible mixtures. Reu-
ben Ottenberg performs the first blood transfusion using blood typing and crossmatching in New York. Ottenberg also observed the Mendelian inheritance of blood groups and recognized the „universal” utility of group O donors [13,14].

Moreschi 1908 was the first one to describe antiglobulin reaction (Coombs-ov test). An antiglobulin test is a way of directly visualizing an antigen-antibody reaction that occurs but cannot be visually detected without the addition of antiglobulin. Antigen on erythrocytes and antibody react with each other, then after washing, unbound antibodies are removed, antiglobulin reagent is added, which binds the antigen-antibody complex on erythrocytes, which makes the reaction visible [15].

In order to keep the blood clinically useful, Dr. Albert Hustin, a Belgian medical doctor, contributed in 1914 to his discovery that sodium citrate prevents blood coagulation and allows blood to be stored outside the human body [16]. All previous procedures for storing blood have enabled short-term storage of blood, in fact, binding of the donor and the patient. It was not until 1916 Francis Rous and J.R.Turner introduce a citrate-glucose solution that permits storage of blood for several days after collection. Allowing blood to be stored in containers for later transfusion aids the transition from the vein-to-vein method to indirect transfusion. This discovery also allows for the establishment of the first blood depot by the British during World War I [5].

In the war year 1915, Dr. Krstić and Dr. Ludvik Hirschfeld gave the first transfusion of fresh blood to a wounded soldier, and a year later a transfusion of canned blood. Thus, in addition to three specialties, surgery, orthopedics and radiology, Dr. Krstić also practised transfusion medicine in that period [9].

Blood banks

During the First World War in 1917, the first blood bank was founded based on the idea of Oswald Hope Robertson, for which he was awarded the 1958 AABB Landsteiner Award. Blood safety for use included sterile bottles, anticoagulant use, syphilis testing, and cold storage [5,17,18].

The British Red Cross as the first human blood transfusion service in the world was instituted in 1926 [5].

The first hospital Institute of Blood Transfusion later named „Blood Bank”, was introduced 1932 in a Leningrad Hospital, Russia. The increase in the number of transfusion procedures indicated the need for longer-term storage of blood, which instigated the Russian doctor Dr. Andrey Bagdasarov Arkadevich in 1932 to develop a way to store blood for 21 days in bottles [4,7].

The International Society of Blood Transfusion (ISBT) was founded in 1935 [4,6].

The Spanish doctor Federic Durán-Jordà 1936 founded the world’s first transfusion center in Barcelona at the beginning of the Spanish Civil War. The idea was spreading and shortly afterwards, the Canadian doctor Normal Bethune founded a similar center in Madrid in 1936 and the first vacuum blood bottle was marketed by Hyland [4,5,7].

America and the UK founded the first hospital blood banks in 1937. The name blood bank comes from Bernard Fantus and the first he founded in Chicago County hospital five years after Russia (SSSR) [7,19].

The outbreak of World War II in 1939 brought a huge need for transfusions and blood donation centers in UK. In 1940 dr Karl Landsteiner and dr Alexander Weiner discovered Rhesus factor [4,6,7].

Edwin Cohn, a professor of biological chemistry at Harvard Medical School, develops cold ethanol fractionation 1940, the process of breaking down plasma into components and products. Albumin, a protein with powerful osmotic properties, plus gamma globulin and fibrinogen are isolated and become available for clinical use. John Elliott develops the first blood container, a vacuum bottle extensively used by the Red Cross [4,6,7].

Mourant, and Race 1945 describe the use of antihuman globulin (later known as the „Coombs Test”) to identify IgG („incomplete”) antibodies [13, 15].

The American Association of Blood Banks (AABB) is formed 1947 [8].

Cryopreservation of blood

Audrey Smith 1950 reports the use of glycerol cryoprotectant for freezing red blood cells, and Carl Walter and W.P. Murphy, Jr., introduce the plastic bag for blood collection. Replacing breakable glass bottles with durable plastic bags allowed for the evolution of a collection system capable of safe and easy preparation of
multiple blood components from a single unit of whole blood, but glass bottles were replaced by plastic blood bags in 1975. Development of the refrigerated centrifuge in 1953 further expedites blood component therapy.

The great progress in the clinical application of transfusion medicine was marked by the following discoveries in the field of transfusion medicine. The AABB published 1958 its first edition of Standards for a Blood Transfusion Service, (now titled Standards for Blood Banks and Transfusion Service. A. Solomon and J.L. Fahey reported the first therapeutic plasmapheresis procedure, a procedure that separates patient’s whole blood into plasma and red blood cells 1960, but plasmapheresis is introduced as a means of collecting donor plasma for fractionation long after in 1964. The role of platelet concentrates in reducing mortality from hemorrhage in cancer patients is recognized in 1961. The first antihemophilic factor (AHF) concentrate to treat coagulation disorders in hemophilia patients was developed through fractionation, 1962. Judith G. Pool and Angela E. Shannon 1965. reported a method for producing Cryoprecipitated AHF for treatment of hemophilia [4,8,11].

Rh immune globulin is commercially introduced to prevent Rh hemolytic disease in the newborns of Rh-negative women 1967, which is the most important turning point in preventing the sensitization of pregnant women and the mortality of newborns [20,21].

The blood establishment has been improved both organizationally and functionally in order to ensure the safest possible blood.

Activities to provide Safer Blood

Blood establishment in 1970s moved toward an all-volunteer blood donor system. A syphilis test was introduced in 1947, and in order to raise the quality of transfusions, in line with European and world trends, mandatory testing of blood donors for HBsAg in 1971 was introduced [7,22].

In the eighties of the twentieth century, the HIV virus was identified and licensed the test for HIV testing. The FDA registered the first ELISA test for HIV antibodies in 1985. In Serbia, testing for the presence of HIV antibodies was introduced in 1987 [4,7]. To provide blood safer for transfusion in 1990, the first specific test for hepatitis C virus was introduced for donors. In 1992 donor testing for HIV and HIV2 antibodies was implemented [4,7]. In 1996 Western blot testing for p 24 HIV antigen begins, which significantly reduces the window period, and in 1999 introduces Nucleic Acid Testing (NAT) testing for HCV and HIV, which reduces the window period. The FDA introduced the application of PCR technology (NAT testing) in 2002 [5,7,24].

Donor cytapheresis was introduced in 1972. The erythrocyte retention period is extended to 42 days with the introduction of the optimal additive solution in 1983. In many countries around the world, the centralization of transfusion centers began in 1996, replacing existing regional centers [7,25].

With the formation of stable blood banks, there was a need for establishing the Guidelines for blood transfusion. The first guidelines were printed in England in 1990. The internationally accepted Guideline for Transfusion „Red Book” was printed in 1990 by HMSO [25,26].

In accordance with the reduction of possible microorganisms present in blood units in 2003, the Guidelines on the implementation of bacteria reduction and detection standard was published, which extended the usability of platelets obtained by apheresis, up to 7 days [25,27]

Clinical transfusion includes the activity of storage and dispensing of blood and blood components for therapeutic use, pre-transfusion tests, care for optimal use of blood and blood components, autologous transfusion, therapeutic apheresis procedures, hemostasis tests, perinatal tests, monitoring the effects of treatment with blood components and is performed in hospital units of clinical transfusion with blood banks [1,28].

The turning point for the organization of hospital blood banks was 1987, when the European directive provided for the gathering of member states on the legal responsibility for blood products, starting in July 1988. So far, 8 editions of the guidelines have been published „Red Book” [26].

By 2020, 20 editions of the Guide to the preparation, use and quality assurance of blood components (Council of Europe) have been published, and in the Republic of Serbia it has been translated and is in use16. 2011 edition [23,24].

Intravascular intrauterine transfusion (IVIUT) into the umbilical cord, was first
Transfusion medicine in Serbia

Using international guides and standards, it can be said that the clinical transfusion of the Republic of Serbia has developed parallel with world trends. The first blood transfusion was performed by Dr. Nikola Krstić in 1915 in the Great War on the Thessaloniki front, when the blood was donated by Budimir Gajić, a Thessaloniki combatant [2,16]; the first independent transfusion cabinet (ITC) was founded by Prof. Dr. Milivoje Kostić in Belgrade in 1934 at the State Hospital. From the end of World War II until today, a network of 52 ITCs has been formed in Serbia [29].

The accelerated development of transfusion medicine in Serbia is taking place in parallel with the world development of transfusion. Promotion of voluntary unpaid donation begins in 1951, current tests for testing and blood control of donors are introduced (Rh testing, direct antiglobulin/Coombs test (DAT/DCT) in 1953 [13,15] isolation of blood components (dry plasma, erythrocytes) and application of targeted chemotherapy (platelets, cryoprecipitate) 1967. In order to raise the quality of transfusion, in accordance with European and world trends. Due to the development of transplantation medicine, HLA typification was introduced in 1972 [30]. In order to obtain a single donor of a blood component, the use of apheresis procedures (thrombocytapheresis and plasmapheresis) began in 1977. Further development of transfusion is through cryopreservation of erythrocytes in 1984. Due to specific population groups (sensitized patients and religious groups), the use of alternatives in transfusion has been developed since 1992 [31]. Isolation and transplantation of hematopoietic stem cells (HSC) was introduced in 1994. The penetration of information technology in transfusion began in 1989 [7].

Routine application of transfusion activities in Serbia went through the establishment of an organized, nationally coordinated Transfusion Service, blood collection exclusively from voluntary, unpaid blood donors from low-risk behavioral populations, efficient testing, processing, storage, distribution and transport of all donated blood, rational and responsible use of blood/products using transfusion alternatives wherever possible - Establishment of a Quality Management System (QMS) in the field of transfusion, throughout the blood chain from donor to patient [32].

EU Directives, Council of Europe, Recommendation

Blood transfusions of European countries have evolved in different directions - transfusion systems of European countries are heterogeneous at the administrative, organizational, medical and scientific levels [33]. Due to the frustrations of many European countries caused by tragedies and traumas that have occurred in transfusion in the past, due to the need to minimize the risks of blood transfusion, due to the right of everyone to receive transsudological treatment of the same quality, the basics of harmonization and standardization of the system blood transfusions in EU countries.


The European Commission operates through recommendations (EC Recommendations) [42], of which the most important in practice are: Recommendation No. R (88) 4, which refers to the responsibility of health authorities in the field of blood transfusion [43]. Recommendation No. R (95) 14. refers to the protection of blood donors and recipients when giving or receiving blood [44] Recommendation No. R (95) 15 contains a technical annex with guides for the preparation, use and quality assurance of blood components. This recommendation is the most widely used and is innovated every year [45]. Recommendation No. R (96) 11 refers to the documentation and storage of data that guarantee the traceability of each unit of blood/product (traceability), especially in hospitals [46]. Recommendation No. R (98) 2 refers to the provision of hematopoietic stem cells. [47]. Recommendation No. R (98) 10 refers to the use of human erythrocytes for the preparation of oxygen-carrying substances [48]. Recommendation No. R (2001) 4 deals with the prevention of possible transmission of the Creutzfeldt - Jakob disease variant by blood transfusion [49], Recommendation No.R (2002) 11 refers to the role of hospitals and clinics in the optimal use of blood/products [50], Recommendation No. R (2003) 11 refers to procedures for inactivating pathogens that can be transferred by blood/products [51], Recommendation No.R (2004) 8 applies to autologous umbilical cord blood banks [52], Recommendation No. R (2004) 18 refers to the education of nurses in the field of transfusion medicine [53], Recommendation No. R (2004) 19 refers to the criteria for the authorization of institutions for organ transplantation [54].

Legislation in Serbia

The development of transfusion medicine in Serbia relied on legislation: the Law on Transfusion Activity [55], and the Conditions are defined by regulations: Rulebook on detailed conditions, standards and measures for establishing a quality system in performing transfusion activities, ie certain transfusion activities [56]; Rulebook on detailed conditions for storage, management and distribution of blood and blood components [57]; Rulebook on detailed conditions regarding personnel, equipment and space for performing transfusion activities, ie certain tasks of transfusion activities [58]; Rulebook on the manner and procedure of keeping and availability of documentation in authorized transfusion institutions, ie hospital blood banks [59]; Rulebook on detailed conditions for testing blood and blood components [60]; Ordinance on the manner and procedure of keeping records in authorized transfusion institutions [61].

Transfusion legislation is alive and flexible, so all these ordinances and laws are united in one law and one ordinance that is in force in the Republic of Serbia today: the Law on Transfusion Medicine which separates authorized transfusion institutions from hospital blood banks (clinical transfusion medicine) [1] and the Rulebook on quality assurance in the field of transfusion medicine [28]. According to the Law and Rulebook there are two separate entity: Blod Establishment and Hospital Blood Bank. Blod Establishment (blood collection system) is centralized. This type of transfusion service organization is under development and time will show its efficiency and sustainability.

Worldwide, transfusion medicine is a subspecialization lasting 1-2 years after specialization in internal medicine, hematology, immunology, pathology, anesthesiology, and pediatrics, and doctors who practice it have different statuses and titles. As an independent specialty, transfusion medicine exists in Germany and Serbia. It has existed as an independent specialization transfusion medicine at the Faculty of Medicine in Belgrade (Serbia) since 1960 [2, 6].

Haemovigilance and PBM

Modern therapeutic procedures include vigilance system, i.e. recording of side effects and patient blood management (PBM). A haemovigilance network has been developed as part of the transfusion. The concepts of national chemovigilance systems in European countries are very different. The European Haemovigilance Network (EHN) was formed in 1998, from which the International Haemovigilance Network was formed later in 2009 (IHN) The network started with five member countries from Europe and it now has 32 international members [62,63,64].

The term Patient Blood Management
was first used in 2005 by Professor James Isbister, an Australian haematologist, who realised that the focus of transfusion medicine should be changed from blood products to the patients. PBM is a multimodal, multidisciplinary patient-centered approach adopted to minimise the use of allogeneic blood components with the aim of improving clinical outcomes of patients. It is especially important for surgical disciplines [65]. In addition to autologous transfusion, PBM implies Blood conservation techniques which encompass four pillars: 1) Optimizing the Hemoglobin/Hematocrit, 2) Minimizing blood loss, 3) Optimizing tissue oxygenation, and 4) Lowering the Transfusion Trigger (increase tolerance of anemia). The effectiveness of PBM has been confirmed in cardiovascular surgery, in gynecology and obstetrics, in orthopedic surgery [66,67,68,69].

Hemovigilance and PBM in Serbia

Hemovigilance in Serbia began in the mid-1990s and consists of the obligation of a competent doctor to report a suspected adverse reaction to a transfusion to the competent hospital transfusion commission, which reports to the Biomedicine Directorate of the Ministry of Health of the Republic of Serbia in accordance with the Law [1]. By consensus, a unified form for reporting on transfusion adverse events and reactions was accepted [22,28]. The Rulebook on Quality Assurance in the Field of Transfusion Medicine defines the monitoring system, reporting method and other issues of importance for the identification of each individual blood sample or individual blood unit, as well as the manner, procedure and content of the form for reporting serious adverse events or serious adverse reactions on the manner and procedure of keeping records in authorized transfusion institutions [1,28].

PBM in Serbia is accepted in tertiary level health care facilities. It is widely accepted in the field of cardiovascular surgery, orthopedics as well as gynecology and obstetrics, and it is performed by transfusiologists and anesthesiologists [70].

In order to further develop transfusion medicine and PBM in Serbia, it is necessary to establish a hospital blood bank in each hospital and clinical center with the possibility of mutual cooperation and strengthen infrastructure and human resources.

CONCLUSION

Regulations The Republic of Serbia is in line with international regulations, Council of Europe regulations and European Union Directives, and as far as the education of doctors is concerned, it belongs to the 3 countries that have profiled clinical transfusiologists in the most professional way.

Authorized transfusion services have been established, where testing for transfusion-transmitted diseases (syphilis, HBV, HCV, HIV) and hospital blood banks is centralized.

The therapeutic shift towards personalized therapy, including stem cell therapy, patient blood management, future development is towards teamwork and interdisciplinary cooperation with clinical pharmacologists, immunologists, toxicologists, hematologists, obstetricians, pediatricians.

Obligatory acquaintance and informing of all health profiles with the regulations in clinical transfusion medicine.

Strengthen infrastructure and human resources in the transfusion service.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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**Transfuzijska medicina - istorijski osvrt i legislativa**

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**KRATAK SADRŽAJ**

**Uvod:** Prošlo je više od 300 godina od prvih pokušaja upotrebe krvi u terapeutske svrhe, do naučno zasnovanih postulata upotrebe krvi. Svaka generacija lekara, suočena sa potrebom za kliničkom transfuzijom radi spasavanja života, doprinela je bezbednosti i prihvatavanju transfuzije rešavajući nedostatak laboratorijske opreme, zakonodavstva, pa čak i adekvatno obučenog medicinskog osoblja. Cilj ustraživanja bio je da se ukaže na istorijski razvoj i na postojeću regulativu za značajnu kliničku oblast, Kliničku transfuziologiju kao posebnu celinu.

**Materijal i metode:** Online pretraga istorijskog i medicinskog razvoja transfuzije i međunarodnih i domaćih propisa iz oblasti transfuziologije. Pretraživanje literature je obavljeno korišćenjem baza podataka PubMed, Cochrane, Embase i Scopus. Pretraga je obavljena po sledećim ključnim rečima: transfuziologija, regulativa, lekarsko obrazovanje, istorija transfuzije.


**Zaključak:** Terapijski pomak ka personalizovanoj terapiji, uključujući terapiju matičnim ćelijama, „patient blood management“, ima budući razvoj u timskom radu i interdisciplinarnoj saradnji sa kliničkim farmakologizma, imunologizma, toksikologizma, hematologizma, akušerima, hirurzima, pedijatrima. Obavezno je upoznavanje svih zdravstvenih profila sa propisima iz kliničke transfuziologije.

**Ključne reči:** transfuzija, regulative, directiva, preporuke, upravljanje krvlju za transfuziju

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