Corey S. Scher · Alan David Kaye
Henry Liu · Seth Perelman
Sarah Leavitt *Editors*

Essentials of Blood Product Management in Anesthesia Practice

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ISBN 978-3-030-59294-3 ISBN 978-3-030-59295-0 (eBook)
https://doi.org/10.1007/978-3-030-59295-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

Blood and blood products have been experimented with and employed to treat clinical disease processes since the early 1600s. Today the indications for the therapeutic use of blood and blood products have expanded significantly. Recent outcome studies have found a wide range of beneficial indications for the use of blood or blood components. Today, in clinics and hospitals worldwide, the patient's own blood is harvested, and components are reinjected strategically to reduce inflammation and promote healing for a wide variety of clinical conditions.

The use and ordering of blood products based on clinical disease processes or procedural necessity can be a complex issue fraught with economic, physiologic, and religious matters. Knowledge of disease processes, patient risk factors, and modern-day testing specificity creates an ever-expanding knowledge base for the practicing clinician. A thorough understanding of standard practice involving appropriate testing, selection, and screening of donors, storage of blood products, compatibility testing, storage of donations, and clinical use indications are all requirements for today's practitioner.

Regarding blood needs and blood supply, the American Red Cross states that someone needs blood in the United States every two seconds, and less than 38% of the population has the ability or is eligible to donate blood or platelets. It is critical for those having surgery, receiving cancer treatment, experiencing a chronic illness, or someone involved in a traumatic injury that an intact blood supply exists. In the United States alone, nearly 21 million blood components are transfused yearly.

This book was created under the leadership of Corey S. Scher, MD, Henry Liu, MD, Seth Perelman, MD, and Alan David Kaye, MD, PhD all of whom are my long-time esteemed colleagues and friends. Together they have worked tirelessly to recruit experts from diverse medical fields and professional disciplines to share their expertise and knowledge in the following chapters. Students and professional practitioners alike will be able to utilize the material in this book both in their medical practice and for continued education. It is my honor to introduce Essentials of Blood Products and my hope that the reader will take deep satisfaction in their efforts to create a timeless volume of information that will continue our shared commitment to the Hippocratic Oath: "To treat the ill to the best of one's ability, to preserve a patient's privacy, to teach the secrets of **medicine** to the next generation, and so on."

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The History of Blood Transfusion and Blood Management

1

Philip G. Boysen II and Douglas R. Bacon

Introduction

Blood was mystery rather than science for thousands of years. Blood, and its function, was surrounded by religious beliefs, rituals, social customs, and human experiences. That blood was a "life force" was obvious. One had only to observe that when blood was drained from humans and animals, weakness and death followed as a result. In every language, blood is used as a symbol for family relationships; being "related by blood" refers to the concept of family ancestry or descent, as opposed to related by marriage. We emphasize bloodlines when we speak of "royal blood," or assert that "blood is thicker than water."

Perhaps the most emphatic statement on the power of blood is made by William Shakespeare in his famous history play, Henry V. King Henry is exhorting his outnumbered, undernourished, fatigued, and diseased soldiers to engage the French forces. He exclaims:

> And Crispin Crispian shall ne'er go by,
> From this day to the ending of the world,
> But we in it shall be remembered-
> We few, we happy few, we **band of brothers,**
> For he today that sheds his blood with me
> Shall be my brother; be he ne'er so vile,
> This day shall gentle his condition;
> And gentlemen in England now-a-bed
> Shall curse themselves they were not here,
> And hold their manhoods cheap whilst any speaks
> That fought with us on Saint Crispin's Day!

The absent historical fact in the play is that the English were trapped. Their retreat to Calais, the embarking point to return to England was blocked by the French. Their position was desperate. But the English had perfected the long bow, with spear-like arrows, allowing the English army to launch a hail of projectiles in rhythm to cut down the French before they were able to engage the battle line. The point is made that spilling blood in desperate battle brings the soldiers as close together as any family tie. For centuries humans really knew nothing about blood, how and where it was made in the body, the actual composition of blood, and its purpose. Accepting it as a life force led to the conclusion that drinking blood or rubbing it on the body would make one stronger. The stronger the animal or human from whence the blood came, the greater the effect. Spectators would rush the field of battle to drink the blood of wounded and slain gladiators to assimilate their courage and strength.

Notable cultural exceptions to the ingestion of blood are found in religious texts. In the Old Testament, Jewish dietary laws forbid consuming blood in even the smallest quantity (Leviticus 17:13). Blood must be purged from meat by salting and soaking in water. However, the next statement (Leviticus 17:14) reasserts the life force of blood: "because the life of every animal in in its blood." Similarly, consumption of food that is contaminated with blood is contrary to Islamic dietary law. "Forbidden to you are dead meat, blood, the flesh of swine, and that on which hath been invoked the name of other than Allah." (Qur'an sura Al-Maida 5:3).

The Legacy of Hippocrates

The teachings of Hippocrates were viable for 2000 years and the basis of Western medicine [1]. His basic theory identified four "humors" operating in the body: health and wellness depended on these four humors operating in balance, a conceptual humoral homeostasis. The four humors were blood, phlegm, yellow bile, and black bile. Hippocrates proposed that no single one of these humors were more important than the other. Well into the Renaissance period, the language of

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A. D. Kaye, S. Leavitt (eds.), *Essentials of Blood Product Management in Anesthesia Practice*,
https://doi.org/10.1007/978-3-030-59295-0_1

humoral theory, *sanguine, phlegmatic, melancholic, and choleric,* indicated which of these humors were out of balance, and the resulting personality and demeanor.

- Sanguine: cheerfully optimistic, hopeful, confident, even arrogant
- Phlegmatic: calm, or even an apathetic temperament
- Melancholic: gloomy, dejected, depressive personality
- Choleric: irritable, easily angered, and unpredictable

Given the physical state associated with the humors, early physicians concluded that the major function of blood was to control one's mental state. Therefore, it followed that "bad blood" could be addressed by bleeding the patient to let the offending humor out of the body.

The ancient Greeks had a limited knowledge of anatomy. Advancing the science of anatomy and physiology would be in direct contradiction to the theory of Hippocrates. However, the legacy of Hippocrates is a positive one. He proposed a holistic view of medicine and the expectation that a physician should be selfless in the care of patients and hold to the highest ethical and moral standard.

Antiquity and the Concept of Transfusion

In antiquity, the first "transfusionist" was Medea, a character in the epic poem by Ovid [2]. She is the protagonist in Metamorphosis, Book VII. Medea is enjoined by her husband Jason to rejuvenate his aging and failing father, Aeson. At first, he begs her to transfer some of his own life-years to his father, a plan which she rejects as offensive to the gods. Her plan is to drain the blood from Aeson and replace it with a secret potion. The ingredients are many and secret:

> Meanwhile the strong potion in the bronze pot is boiling and leaping, and frothing white with swollen foam… and wherever the froth bubbled over from the hot pot and fell upon ground the earth grew green and flowers and grass sprang up. When she saw this Media unsheathed her knife and cut the old man's throat; then letting the blood run out, filled his veins with her brew… his beard and hair lost their hoary gray and became black again; his leanness vanished, away went the pallor and look of neglect, deep wrinkles were filled out with new flesh, his limbs had the strength of youth.

Medea is described as moving round the "blazing altar" while dipping many cleft sticks in the dark pools of blood, to which she added a long list of additional ingredients including animal organs and parts.

When the daughters of King Pelias heard of this achievement, they begged Media to similarly rejuvenate their father. Media used this art and sorcery as a method for murder. She scolded the daughters.

> Why do you hesitate now, you laggards? Come now, draw your swords and let out his blood that I may fill his veins with young blood again!

The daughters set upon the father, their king, stabbing him repeatedly, but when the time came for the rejuvenation, Medea was nowhere to be found, and the two daughters realized they had murdered their father.

The Discovery of the Circulation

The physiology of blood and circulation was hampered by slow discovery of human anatomy, and incorrect assumptions. The first known treatise on circulation is found in the Ebers Papyrus, a book of medical knowledge written in the sixteenth century B.C. [2]. Although mainly concentrating on remedies and "prescriptions" of the day, it asserts the connection of arteries to veins, but believed the circulatory system carried air and not blood. Air entrained from the atmosphere was thought to enter both the lungs and the heart.

The circulation of vital fluids in the body was described in the *Sushruta Samhita,* sixth century B.C., describing the arteries as channels [3]. Sushruta also understood the valves of the heart had something to do with directional flow of vital fluids, but did not offer complete understanding of how that function was achieved. The concept of arteries, veins, and blood therein was misunderstood due to lack of anatomical study and cadaveric dissection. After death, the veins' arteries appear empty, and the assumption was made that in life arteries and veins carried air. Three specific errors, all proposed by Aristotle, and physicians of his time, led to three misconceptions:

1. Aristotle opined the arteries carried air not blood.
2. Veins carried blood to the extremities, not from them.
3. The interventricular septum separated right ventricle from left, but the septum had pores or perforations.

Greek physician Herophilus is the first true anatomist, and has been dubbed the "father of anatomy" [4]. As a young man, he emigrated to Alexandria, the most progressive city in the world during the reign of the Ptolemaic Pharaohs [5]. The city collected books as well as scholars of all sorts. With the death of Alexander the Great in 325 B.C., the leadership void was filled by one of his general who took the name Ptolemy, and his dynasty was in power from 305 B.C. to 30 B.C. During that time, all the Pharaohs took the name Ptolemy, and all the Ptolemaic queens regnant became Cleopatra, Arsinoe, or Berenice. Cleopatra VII was the last ruler of the dynasty when Romans captured the city in 30 B.C. During this period of academic enlightenment, Herophilus practiced dissection for an estimated 30–40 years. At some point, he was accused of vivisection of prisoners, but this was probably a false accusation. He still believed that the vascular system carried air not blood, and would have corrected that error in thinking had he been performing vivisection. With the passing of the Ptolemaic dynasty,

cadaveric dissection was abandoned for the next 1800 years, restarting in the middle of the sixteenth century.

The Greek physician Galen corrected the first error in thinking in the second century A.D. He established the fact that arterial blood was a brighter red color than the darker hue of venous blood. He established two separate functions for arterial versus venous blood, different and unrelated [6]. Venous blood, responsible for growth and energy, was created from chyle in the liver. Arterial blood was created in the heart, and its function was to carry air. Blood flowed from the arterial and venous system to the periphery and all organs, there to be dissipated and not returned. Thus, the heart was not a pump, there was no venous return of blood to the heart, and the interventricular septum had pores to allow venous blood to pass from the left ventricle to the right ventricle.

The false assumption of pores in the ventricular septum of the heart was corrected by the Arabic physician Ibn al-Nafis in 1242 [7]. His manuscript was discovered in 1924 in the Prussian State Library in Berlin. In that document, he states:

> …the blood from the right chamber of the heart must arrive at the left chamber, but there is no direct pathway between them. The thick septum of the heart is not perforated and does not have visible pores as some people have thought or invisible pores as Galen thought. The blood from the right chamber must flow through the vena arteriosa (pulmonary artery) to the lungs, spread through its substances, be mingled there with air, passed through arteria venosa (pulmonary vein) to reach the left chamber of the heart, and there form the vital spirit…

So, the assumed perforation in the ventricle of the heart did not exist and blood went through the pulmonary circulation and parenchyma, and returned to the left side of the heart (Fig. 1.1). Ibn al-Nafis and his work were largely unknown for three centuries in Europe. It was again described in 1552 in Spain, and in 1558 in Italy. During that same time, Andrea Cesalpino coined the term "circulation," postulating that the arteries and veins were connected by a thin vascular network [8].

Finally, the English physician William Harvey put it all together [9]. In 1628, he published Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus. The *magnus opus*, a book of 100 pages, was widely read and rapidly influenced thinking. He described the true function of the cardiac and venous valves, and asserted that the arterial pulsation is only due to blood. He did not mention the capillary system, the network connecting arteries and veins, and elucidated by Marcello Malpighi [10].

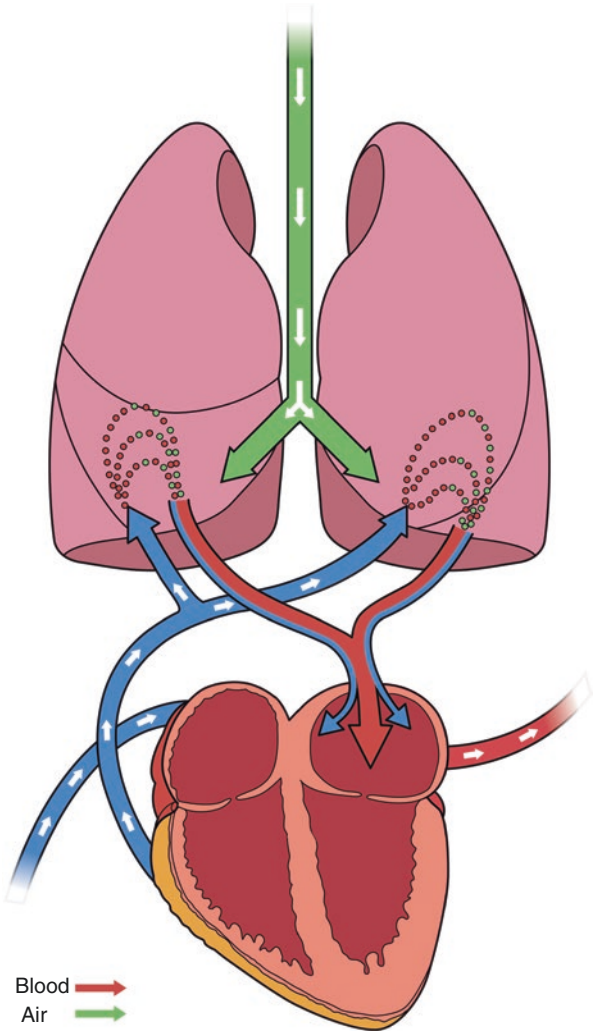

Fig. 1.1 A representation of the pulmonary circulation as described in his writings c. 1236 A.D. [11]

The Cellular Elements of Blood

The microscope became available in the mid-seventeenth century, a Dutch biologist reported its use to study amphibian blood in 1658, and with this instrument gave the first report describing the red blood cell [12]. Unaware of this report by Jan Swammerdam, the Dutch physician Anton von Leeuwenhoek made a second report 16 years later, in 1674 [13].

Nearly 200 years later, the first microscopic description of the platelet was published in the journal *Archiv fur mikroscopische Anatomie.* The journal was founded by the German anatomist Max Schultze 1865, and he published his work in the first issue of his own journal. In his investigation, he describes another component of blood which he dubbed "spherules," later known as platelets. Further he noted these spherules often occurred in clumps and seemed to collect fibrous material [14].

Giulio Bizzozero developed a microscopic technique to examine red blood cells passing in single file in an amphibian web using a live animal. He confirmed the description Schultze made of platelets and also confirmed their role in coagulation at a site of injury [15].

The work of Paul Ehrlich, German physician, was a giant leap forward for hematology. He developed dyes to stain blood smeared on a glass plate. With his dyes he not only garnered information on the red blood cell, but described the white blood cell, clearly showing the difference between lymphocytes and granulocytes [16]. He was awarded the Nobel Prize for these investigations. Finally, and much later, Dr. Max Perutz described the structure of hemoglobin in 1959 [17].

The Royal Society Transfusion Experiments

The Royal Society was founded in London in 1661, obtaining a Royal Charter in 1662 [18]. Among the early founders and participants were Thomas Willis, Christopher Wren, Richard Lower, Robert Hooke, Robert Boyle, Sir William Petty, Thomas Sydenham, and Samuel Pepys. Although other Europeans (Italian, French, and English) wrote about transfusion as a concept, the first documented transfusion belongs to Christopher Wren who employed an animal bladder and two quills to establish a circulatory connection. The knighted Sir Christopher Wren is better known for his contributions to astronomy and architecture. Wren's experiments were later described by Robert Boyle when he published "The Usefulness of Experimental Philosophy" in 1663 [19].

Another member of the Royal Society, Cornish physician Dr. Richard Lower, made a significant contribution of transfusion science in February in the year 1665 [20]. He described the first animal to animal transfusion using a bled dog and transfusing blood from another dog. The first dog was bled to the point of being in extremis, then revived by blood transfusion. He described his work in his book "Tractatus de Corde" published in 1669, his work previously having been read to the Royal Society by Robert Boyle [21].

Lower published the first description of direct transfusion from donor artery to recipient vein after he was unsuccessful in transfusing from vein to vein. This blood transfer failed due to clotting before it could be completed. Of further significance is his ability to use transfusion to replace blood lost for whatever reason, in an era when blood transfusion was viewed as therapy for mental disorders.

Nevertheless, when Lower pushed his technique even further to achieve transfusion from animal to man, he selected a mental patient for the procedure. Arthur Coga, a 32 year-old man, was suffering from anxiety and depression, apparently without benefit from any therapy (including presumably blood-letting). Lower enlisted Dr. Edmund King, a well-known surgeon, to establish the connection from the carotid artery of a sheep to one of Coga's arms. The operation was a success, but the patient showed minimal or no improvement in his mental state. A second transfusion was scheduled but never took place.

A young French physician, Dr. Jean Baptiste Denys, in the employ of King Louis XIV, read of Lower's experiments. He had been experimenting with animal to animal transfusion with the cooperation with his own surgical associate, Dr. Paul Emmerz. He was asked to treat a 15-year old boy who had been suffering with fever for months, again with no improvement after being bled multiple times. In this procedure, the boy was transfused 9 ounce of sheep blood, having been first bled by that same amount. Except for feeling local heat in his arm, the patient tolerated the transfusion but again with little apparent benefit. Denys is credited with performing the first animal to man transfusion in 1667 [22].

Denys continued to expand his transfusion practice using sheep's blood so as not to transmit vices or passions from one human to another. He eventually became aware of the erratic behavior of Antoine Mauroy following a display of public nudity causing his wife to seek Denys in hopes of a cure by transfusion. Denys could not resist this challenge and transfused a small amount of calf blood to Mr. Mauroy, noting no apparent complication or benefit. Within two days, Mauroy transfused the man again resulting in what is now a classic description of a transfusion reaction including hematuria. Denys mistakenly mistook hemoglobinuria as proof of release of "black choler" and a positive sign that his brain would be favorably changed.

However, several months later, Mauroy was irrational and violent, and he was subjected to another transfusion. It was never performed as adequate blood flow could not be established. Mauroy died the following evening. The medical community persuaded the widow to file charges against Drs. Denys and Emmerz. Many physicians of the day still refused to believe Harvey's demonstration of blood circulation; also, the practice of the day continued to bleed patients to remove bad humors in the body. Denys filed his own lawsuit against the widow and had his day in court. He was acquitted when it was discovered that the man had died of arsenic poisoning and the widow confessed!

With his macabre ending came a serious and unfortunate outcome. The Faculty of Medicine of Paris issued a decree that transfusion could not be performed without the permission of a member of the Faculty, which would never be forthcoming. Then in 1678, the French Parliament decreed that transfusion henceforth would be a criminal act. A year later the Royal Society in London followed suit, and wanted nothing to do with the public outcry against the procedure. For the next 150 years, the practice of transfusion was prohibited by law in France and England.

James Blundell and Obstetricians Revive Transfusion Medicine

James Blundell was the first to transfuse human blood (1818) and has been referred to as the father of modern blood transfusion [23]. He was motivated to save women from fatal hemorrhage during childbirth. He also developed a science

of transfusion while reawakening interest in the technique. He had first repeated the experiments of Lower by transfusing exsanguinated dogs. He established that transfusing blood from another dog to the exsanguinated dog was not accomplished without complications, and decided to investigate human to human transfusion. He was the first investigator to wonder about availability of a suitable donor (in this case a dog) to accomplish an emergency transfusion [23].

Blundell was aware of the work of one of his contemporaries, John Henry Leacock who asserted that transfusion is life-saving in the face of acute blood loss, such as the bleeding parturient or wounded soldiers, rather than transfusing for mental disorders.

Blundell had a mechanical mind, and in 1824, published a book introducing a device he called an "impellor" consisting of a funnel to collect donor blood, a surrounding water bath to keep the blood warm, and tubing to push the blood into the patient. A subsequent invention, known as the "Gravitator" provided enhanced blood delivery [24]. An illustration published in 1829 shows a standing donor watching his blood flow into the Gravitator (Fig. 1.2).

In his reports, Blundell noted that some patients reported fever, backache, headache, and passed dark urine, presumably due to transfusion with ABO-incompatible blood.

The Legacy of Karl Landsteiner

Karl Landsteiner (Fig. 1.3) investigated the problem of blood incompatibility, working along the same scientific observations started by Blundell. When he began his work the issue of blood incompatibility was recognized between species, but not within any given species. Landois published a manuscript, "Die Transfusion des Blutes" in 1875 demonstrating that mixing blood from one animal with the blood of another species caused coagulation and lysis

Fig. 1.2 Blood transfusion with the Gravitator, shown in *Lancet* (1828)

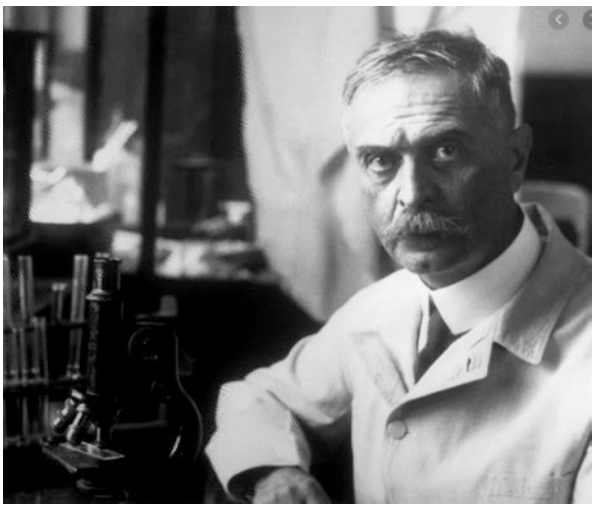

Fig. 1.3 Karl Landsteiner

within minutes [25]. Then 25 years later, Landsteiner did similar experiments limited to human blood. He described his results when mixing red blood cells and serum in 22 subjects. He made two important observations, the first being that clumping of the mixed blood was observed in some specimens but not in others (the blood mixed was "compatible"), and secondly that this was an immunologic phenomenon. He was able to identify three blood groups, A, B, and C [26]. The following year two of his students studied 4.155 patients who had no agglutinins in their own serum, but all three of the previously discovered blood types (group AB). Further they noted that isoagglutinins were present in healthy people and not associated with a disease state [25]. Written in German, Landsteiner's work was not put into common practice until the 1920s. He received the Nobel Prize for his work in 1930 [27].

In that interim, other groups were duplicating his findings unknowingly. Moss described four groups also by naming them in reverse order: IV, III, II, I [28]. It took a meeting of the Congress of the International Society of Blood Transfusion in 1937 to adopt the ABO terminology. Genetic aspects of blood formation and blood inheritance were under investigation since the 1920s racial distribution of blood groups was documented during World War II in Germany [29]. Blood discrimination followed as blood group A was determined to be of Aryan descent, and blood group was a marker for Jewish and Slavic descent. Similarly, in the United States, blood was segregated according to donor by the American Red Cross. Blood from black donors was not acceptable for pooled plasma from which albumin was derived. Such laws were in place in the United States until the late 1960s. In fact, in the 1950s, a law was passed in Louisiana charging physicians with a misdemeanor if blood from a black donor was transfused into a Caucasian without explicit and informed consent. The law remained in effect until it was repealed in 1983 [30].

Another of Landsteiner's students, Philip Levine began work with him in the Rockefeller Institute in 1925. Levine published a case report of a couple, both with blood group O, experienced a bleeding episode after the husband's blood was transfused into the wife. The ensuing post-transfusion hemolysis was investigated by incubating the husband's blood with the wife's blood, which resulted in immediate agglutination. Levine then incubated the woman's blood with 140 compatible samples of ABO blood. Agglutination was observed in 80 samples, thus demonstrating the presence of what came to be known as Rhesus antibodies [31]. The antibodies were so named due to previous work that Levine had performed with Landsteiner that had similar results and did involve Rhesus monkeys. Sir Ronald Fisher, a Cambridge geneticist, established the complexity of the Rh antibody describing several alleles, which he named C and c, D and d, E and e.

In the ensuing years, researchers discovered many new antigens in blood. Coombs developed the anti globulin test to identify new antigenic systems often named for the first patient who had those new antibodies [32]. Further progress was made when Morton and Pickles discovered that enzymes such as trypsin could be incubated with blood to enhance antigenic expression [33]. Coombs identified the Kell antigens in a case of hemolytic disease of the newborn that could not be explained by the Rh antibody. Joseph Duffy (Fy) was a hemophiliac who received multiple transfusion and carried the gene. Mrs. Kidd (Jk) delivered a son, her fifth child, who had hemolytic disease of the newborn. An antibody in her blood agglutinated the blood of 146/189 donors [34].

The Search for an Anticoagulant

Further limiting transfusion medicine was the vexing problem of blood coagulation, which resulted in the requirement of fresh blood for transfusion and donor and recipient in the same place and at the same time. An early approach to this problem was the arterio-venous anastomosis first described in 1913 by the French surgeon Alexis Carrel, a donor radial artery to recipient vein graft. Once again, the immediacy and emergency of the situation involved a mother who had delivered a baby with erythroblastosis fetalis. Carrel was rewarded the Nobel Prize in Medicine for his work [35]. However, the technique has definite limitations. Donor and recipient must be immediately present for the procedure. It is not possible to know how much blood is being transfused, or even to estimate the volume. The blood vessels of donor and recipient could not be used a second time.

A second technique was simply to defibrinate the blood by collecting it into a reservoir and stir with a device to promote clotting, lift out the clot, and use the remaining fluid for transfusion. Prevost and Dumas used defibrillated blood to resuscitate animals that had been exsanguinated and reported their results in 1821 [36]. They also reported severe febrile reactions after the transfusion. What was needed was a third option, i.e., find a stable non toxic anticoagulated environment so that blood could be collected and stored for a prolonged period of time.

The British obstetrician Braxton-Hicks tested a phosphate of soda as an anticoagulant, but it proved to be a toxic medium [37]. Richard Lewinsohn experimented with sodium citrate at a concentration of 1%, noting that some laboratories used it as an anticoagulant for specimens not collected for transfusion as the solution was also toxic. Lewinsohn continued his work, exploring the theory that a lower concentration of citrate might provide anticoagulation without ensuing toxicity [38]. Finally, in 1915, he published his results using 0.2% citrated solution with good anticoagulant effect and no toxicity even if 2500 cc of blood was transfused [38]. But the blood still had to be stored for only a short time. Adding dextrose to stored blood extended red cell survival to two weeks; acid-citrate-dextrose (ACD) improved red blood survival without effect of acid–base milieu in the recipient [39]. Citrate-phosphate-dextrose (CPD) extended red blood cell survival to 28 days [40, 41].

The ability to store blood in a non toxic solution and the ability to prevent coagulation were major achievements in the transition to blood management. Prior to that the blood service concentrated on enlisting donors who had been processed and examined, and able to respond to the need for blood donation in short notice. The first blood service was established in 1921 by Percy Oliver, a civil servant working with the British Red Cross [42]. Establishing a list of prospective donors was a slow process, but the need was evident in post-war England. There were few homes with phones, so the donors were summoned by police and escorted to the facility. The blood donor service expanded throughout the UK in spite of resistance by some physicians to use anticoagulants, and the challenge of having to perform a surgical procedure to access the vascular anatomy. There were still deaths resulting from ABO incompatibility since blood typing was not widely available. The process of enlisting a panel of donors, in essence a "walking blood bank" continues to exist in the American military, and has recently been activated by US Navy physician and corpsmen in a desert post [43]. Eventually, the term "blood bank" meant a physical space, not a living person. Dr. John Lundy at the Mayo Clinic initiated blood banking in 1935 [44]. In 1937, Bernard Fantus opened a blood bank at the Hektoen Institute of Cook County Hospital in Chicago, storing refrigerated blood in bottles for 10 days prior to infusion [45]. Whether blood is collected at the site of transfusion, or collected and stored for later use, a panel of donors is still a requisite.

The shortage of blood donors in Russia in the 1930s demanded a different approach and the result was the col-

lection of cadaveric blood [46, 47]. The premise was that rapid access to a trauma patient, and drainage of blood from a dead donor from the inferior vena cava would result in an adequate amount of blood for transfusion. Shamov reported transfusion of blood from trauma patients and patients who died from cardiac arrest in 2500 recipients with only seven deaths. In the United States, Dr. Jack Kevorkian (who later became famous for his work in physician-assisted suicide) reported similar results [48]. Other physicians collected and transfused placental blood, which was plentiful, but more likely to be infected prior to transfusion [49]. The establishment of blood banks supplanted the use of these and other techniques [50].

Fractionated Blood Products

The fact that blood contains cellular elements and platelets was well established. It wasn't until 1940 that Professor Edwin Cohn, a physical chemist at Harvard Medical School, began to methodically search for other "fractions" in blood and plasma. His technique involved repeatedly exposing blood to ethyl alcohol. With each iteration of the experiment, he varied salt content, temperature, and pH [51]. The isolated fraction I contained mostly fibrinogen, fractions II and III were mainly globulins, and fraction V was albumin. The albumin-rich factor V was reported to restore circulation in accident victims with "circulatory collapse." On December 7, 1941 – the date of the Japanese attack on Pearl Harbor, albumin was immediately deployed to the base and infused into 84 victims, mainly burn injuries with reported improvement enhancing survival. Albumin was introduced into clinical medicine with no randomized clinical trials as would be required today [52].

Immunoglobulins in fractions II and III were employed to provide prevention infectious diseases including measles and Rh hemolytic syndrome [52]. The anti-Rh(D) given by IM injection in male volunteers coated Rh erythrocytes that had been previously injected. Subsequently a combined study between the United States and UK found efficacy in the protection of Rh-negative parturients [53].

Fractionation of blood and treatment of hemophilia is a crowning achievement in modern medicine. Before such treatment became available, young boys died prior to adolescence [54]. Inbreeding of Royal families of Europe who carried the gene for hemophilia saw their line die out due to the disease. Up until the 1950s, bovine and porcine plasma were used to treat hemophiliacs since both were rich in the missing factor, or factor VIII [55]. Severe allergic reactions were noted with repeated exposure stimulating further research [56].

Dr. Judith Graham Poole of Stanford University discovered cryoprecipitate in 1965 noting much greater clotting activity than plasma [57]. Stored in a refrigerator, it could be thawed and administered by a physician [58].

Dr. Kenneth Merle Brinkhous of the University of North Carolina at Chapel Hill discovered the factor VIII deficiency which was responsible for hemophilia in 1935. He later described von Willebrand's disease [59]. Another form of hemophilia, deficiency of clotting factor IX was discovered in 1952 [60].

Blood Management in the Modern Era

It took centuries to develop the concept and practicality of human blood transfusion as a means of treating anemia and blood loss rather than transfusing to treat mental disorders. Safe collection of blood, and storage for prolonged periods, prevention of coagulation, and the fractionation of non-cellular components led to the ability to "manage" the product and extend the ability to treat more patients with a targeted approach to therapy. Subsequent acquisition of knowledge during the past 50 years has been impressive.

- 1967: Rh immune globulin was released as a commercial product
- 1969: Platelet storage at room temperature was reported
- 1970: Blood was collected only from volunteer donors
- 1972: Apheresis is introduced to extract donor platelets, returning the rest of blood
- 1981: Gay Related Immune Deficiency Syndrome (GRID) reported
- 1983: GRID, now AIDS virus isolated at Pasteur Institute in France
- 1985: ELISA test applied to blood donors to detect AIS virus
- 1987: Indirect screening for hepatitis B introduced
- 1990: Testing for Non A–Non B (now hepatitis C) introduced
- 1992: Donor blood now direct testing for HIV-1 and HIV-2 virus
- 1996: Testing for HIVp24 antigen introduced

In addition to addressing hepatitis A, B, C and AIDS, the technology is introduced to screen for and diagnose malaria, toxoplasmosis gondii, and cytomegalovirus. The search for a technique to perform "blood less" surgery has been partially achieved by autologous transfusion, a technology that retrieves the patient's own blood during the surgical procedure, processes it through a "cell saver" to be reinfused into the patient prior to the end of the procedure [61, 62].

The Future of Blood Management

Implementation of blood management has been made possible due to recent advances. The triggers for transfusion have been re-examined and are based on individual patient physiology rather than absolute rules. Rapid assessment of clot formation and fibrinolysis is available using thromboelastography leading to precise replacement of red blood cells, platelets, and blood products. The search for substitutes for hemoglobin and platelets continues. Genetic approaches have been under evaluation such as experiments with transgenic livestock and cultivation of stem cells to grow cellular components of blood. The Joint Commission offers certification in blood management as a means of maximizing the benefit of the resources collected from volunteer blood donors. The search for a hemoglobin substitute continues. The need for blood and blood products, however, will continue for decades to come [63].

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Modern Blood Banking

2

Louise Helander and Caroline Raasch Alquist

Abbreviations

AABB	formerly the American Association of Blood Banks
AIDS	Acquired Immunodeficiency Syndrome
C:T ratio	Crossmatch-to-transfusion (C:T) ratios
CJD	Creutzfeldt–Jakob disease
DAT	Direct antiglobulin test
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FNHTR	Febrile non hemolytic transfusion reaction
HDFN	Hemolytic disease of the fetus and newborn
HLA	Human leukocyte antigens
HPA	Human platelet alloantigens
HTR	Hemolytic transfusion reaction
MHC	Major Histocompatibility Complex
NAIT	Neonatal alloimmune thrombocytopenia
PRT	Pathogen reduction technologies
RBC	Red blood cell
RhD	D antigen of Rh blood group
TA-GVHD	Transfusion-associated graft-versus-host disease
TRALI	Transfusion-related acute lung injury

The ABO and Rh Blood System

The ABO antigens are recognized as the most clinically significant blood group system. Two antigens, A and B, determine ABO typing. The presence or absence of these two antigens create the four common blood group phenotypes: A, B, AB, and O. These antigens are found on red blood cell membranes, lymphocytes, platelets, vascular endothelium, and a wide variety of other tissues. In predisposed type A, B, or AB individuals, antigens are secreted in body fluids, with the exception of cerebrospinal fluid [1]. Those with group O blood type produce a nonfunctional enzyme, which is responsible for the constitutive absence of A and B antigens. ABO phenotypes vary with race and ethnicity (Table 2.1).

Inversely correlated to the expression of A and B antigens, are the expression of anti-A and anti-B antibodies (Table 2.2). Group A, B, and AB individuals express predominantly IgM antibodies. These antibodies are said to be "naturally occurring" because they do not require exposure to a reciprocal antigen for formation. For example, a group A

Table 2.1 ABO & RH phenotypes by race (%)

–	O	A	B	AB	D Pos	D Neg
White	45	40	11	4	83	17
Black	50	40	11	4	93	7
Hispanic	56.5	31	10	2.5	93	7
Asian	40	28	25	7	98	2
Donors	47	37	12	4	85	15

Adapted from Garretty et al. [5]
Decimals have been rounded to the nearest whole number

Table 2.2 ABO antigens and antibodies

Antigens on RBCs[a]			Antibodies in plasma/serum[b]		
A	B	D	Anti-A	Anti-B	Interpretation
0	0	0	+	+	O Neg
+	0	+	0	+	A Pos
0	+	0	+	0	B Neg
+	+	+	0	0	AB Pos

[a]Forward/Front type: Patient RBCs with reagent antisera containing antigen antibodies
[b]Reverse/Back type: Patient serum with reagent RBCs with known antigens added

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A. D. Kaye, S. Leavitt (eds.), *Essentials of Blood Product Management in Anesthesia Practice*,
https://doi.org/10.1007/978-3-030-59295-0_2

individuals will produce anti-B antibodies in their serum as early as three months of age [2]. It is hypothesized that these naturally occurring antibodies are formed in response to environmental and gastrointestinal flora that form structures similar to the ABO antigens and elicit an immune response [2]. The anti-A and anti-B antibodies can agglutinate or cause red cell clumping at room temperature (20–24 °C) and can activate the complement cascade at 37 °C, causing red cell hemolysis.

In contrast, group O individuals express predominantly IgG anti-A and anti-B antibodies. Similar to IgM antibodies, these are capable of activating complement and causing hemolysis. Additionally, group O individuals possess IgG anti-A,B. This unique antibody is believed to react with a common region on the A and B antigens of A, B, or AB individuals, leading to hemolysis [2]. Unlike IgM antibodies, IgG immunoglobulins can cross the placenta and are responsible for the higher rates of hemolytic disease of the fetus and newborn (HDFN) seen in group O pregnant women (see Chapter 23).

The Rh antigens are the second most significant group after the ABO blood system. Originally discovered in 1939 [1], the Rh group is composed of 61 different antigens. Of these, D, C, c, E, and e are known as the primary antigens. Rh genes are closely linked and inherited as a group on chromosome 1. This system is considered to be the most immunogenic of all the minor blood group antigens, with the D-antigen (RhD) being the most immunogenic and clinically significant of the group [3, 4]. "Rh-positive" and "Rh-negative" terminology is generally accepted as denoting the RhD antigen status of a patient. Using "RhD-positive" or "RhD-negative" terminology when referring to a RBC unit is more accurate.

Unlike ABO antibodies, anti-RhD antibodies require exposure to D-antigen for formation. They are predominantly IgG antibodies which can bind and agglutinate red blood cells, leading to extravascular hemolysis. RhD antibodies do not typically activate complement. As with the ABO system, phenotype frequency varies by race and ethnicity. Overall, roughly 85% of individuals are classified as RhD-antigen positive [1, 5].

ABO group and RhD testing of donated blood is performed after collection. Additionally, the ABO group and RhD-negative status of all products containing red cells (RBCs, whole blood, and granulocytes) must be confirmed by the receiving hospital prior to use [2]. Testing consists of typing for antigens attached to the red blood cell membrane with antigen-specific reagent (forward type), as well as screening for suspended antibodies in serum or plasma with antigen-positive test cells (reverse type).

Similarly, prior to routine transfusion, a patient's ABO and RhD type must be confirmed with forward and reverse typing. ABO type in this setting must be confirmed by two determinations prior to transfusion. A second determination can consist of comparison to previous records, testing a second patient sample, or retesting of the same sample if the patient's identity was verified with a validated process to reduce misidentification [6]. This check helps ensure that donor RBCs will be compatible with the recipient's plasma to minimize the risk of life-threatening hemolysis.

Table 2.3 Compatible recipients and donor units

Recipient ABO/Rh type	Compatible RBC units	Compatible platelet units	Compatible plasma units[a]
O -	O –	Platelets are not ABO or Rh matched	O, A, B, AB
A +	O +, A +		A, AB
B +	O –, B –		B, AB
AB +	O +, A +, B +, AB +		AB

Adapted from Technical Manual, Nineteenth Edition
[a]Plasma does not need to be Rh matched

A RBC unit is compatible if the ABO and Rh antibodies in the recipient's serum will not react with antigens on the donor's cells. For example, a group A recipient with anti-B antibodies in their serum would likely be compatible with a group A donor (same type) or with a group O donor whose red blood cells lack A and B antigens to be acted on by the anti-B antibodies. Group O red cells and platelets lack ABO surface antigens and are referred to as universal donor cells. Conversely, group O plasma containing IgG anti-A,B and IgM anti-A and -B is not compatible with Group A or B recipients. Group AB individuals lack ABO antibodies in their serum, making AB plasma products compatible with any blood group recipient. Group AB individuals can receive RBC-containing products from any ABO blood group (Table 2.3). Please note that these examples only hold true in the absence of recipient alloimmunization, further discussed below.

In the absence of a confirmed patient ABO typing during emergent situations, group O RBCs can be safely used. The RhD antigen status of products selected for emergent transfusion may vary by patient type. Similarly, either group AB or A plasma products may be issued for transfusion in emergency settings with unknown recipient ABO and RhD typing. These two notable exceptions to historic blood bank dogma are discussed below in the Inventory Management section.

Other Blood Antigen Systems

Beyond ABO groups and the Rh system, over 350 additional RBC antigens have been identified [7]. Only some are considered clinically significant and capable of causing hemolysis, HDFN, and reduced RBC survival [8]. Clinically insignificant RBC antigens have little to no clinical conse-

quences when transfused to alloimmunized recipients. Red cell antibodies are typically IgG and are regularly screened for in standard patient antibody screen testing [6, 7, 9]. This testing uses recipient serum or plasma and watches for agglutination with screening red blood cells of known antigen type. If a screening cell agglutinates with the recipient serum or plasma, additional work up is warranted to identify the specific antibody/antibodies. If clinically significant antibodies are identified, the patient will need to receive cross-match-compatible red blood cells that lack the corresponding antigen [6].

The Human Leukocyte Antigen System

The human leukocyte antigen (HLA) system is encoded by a group of closely linked genes located on chromosome 6 in a region known as the major histocompatibility complex (MHC). HLA antigens have an essential immune function in the binding and presentation of antigens for T cell recognition [10]. Because we develop tolerance to our own HLA type, our immune system can identify non self cells within the body by their foreign HLA antigens [10]. For the purposes of transfusion medicine, Class I and Class II are significant for transfusion management.

Class I antigens are found on the surface of all nucleated cells in the body, including platelets, the products of nucleated megakaryocytes. Immature nucleated RBCs also express HLA antigens. These are generally lost in maturation with the exception of Bennett-Goodspeed (Bg) antigens, Class I HLA antigens retained on mature red cell membranes [11]. Class II antigens are found on antigen-presenting cells, including B-lymphocytes, monocytes, macrophages, dendritic cells, and activated T-lymphocytes. Class I and II HLA antigens and antibodies are of particular importance when selecting appropriate platelet and plasma donor units.

Platelets carry Class I HLA antigens, in addition to ABO antigens and human platelet alloantigens (HPA). They do not express Rh or Class II HLA antigens. Given a short shelf life of 5–7 days and commonly limited inventory (see Chapter 3: Component Therapy), platelet units may be transfused without matching for ABO, HLA, or HPA status. ABO, HLA, or HPA-incompatible units may be associated with a lower platelet number increases following transfusion, but this has not been shown to have a measurable impact on clinical bleeding [12]. As an exception to this rule, if a patient demonstrates significant platelet transfusion refractoriness on two occasions and non immune mechanisms (e.g., fever, hypersplenism, or sepsis) are ruled out, HLA and HPA antibodies must be considered [13]. HLA antigens are the most common cause of immune-mediated refractoriness [13]. Consulting with the Transfusion Medicine Service or blood bank can help clarify the need for additional HLA antibody testing and subsequent HLA-matched product requests in select individuals.

HLA antigens are also implicated in transfusion reactions. Plasma products are a suspension of proteins, immunoglobulins, coagulation factors, and a multitude of other dissolved substances necessary for cellular metabolism. HLA antibodies may be included in this suspension, which can result in HLA antibody-mediated transfusion reactions. Transfusion of plasma-containing products, which may harbor HLA antibody, have the potential to cause transfusion-related acute lung injury (TRALI). Leukocytes with HLA Class I and II antigens are commonly found in cellular blood products, which have the potential to cause HLA-mediated febrile non hemolytic transfusion reaction (FNHTR), rare hemolytic transfusion reactions (HTR), potentially fatal transfusion-associated graft versus host disease (TA-GVHD), as well as TRALI [14, 15]. All transfusion reactions are described in greater detail in Chapter 12: Complications of Blood Transfusions.

In the event of a transfusion reaction, the transfusion must be stopped immediately and a workup is required [14]. The initial work up steps include checking all clerical work for errors, retyping the patient ABO, visually assessing for plasma discoloration indicative of hemolysis, and performing a direct antiglobulin test (DAT) [14]. The DAT can help distinguish immune from non immune-mediated hemolysis causes and is also used in HDFN and autoimmune hemolytic anemia workups. The DAT can determine if an individual's RBCs are coated with immunoglobulin and/or complement. An appropriate specimen must be received in an ethylenediaminetetraacetic acid (EDTA) tube, to chelate calcium from the sample and stop the in-vitro fixation of complement, which could cause a false-positive result. Unfortunately, there are many causes of a false-positive DAT (infections, high serum immunoglobulins, antiphospholipid syndrome, medications), and up to 15% of hospitalized patients with no signs of hemolysis will have a positive test [16]. A positive DAT is therefore not diagnostic of hemolytic anemia, but must be examined in the context of the patient's diagnoses, medication history, pregnancy status, and transfusion history. If the work up rules out hemolysis, other etiologies must be investigated to classify the transfusion reaction [15].

Alloimmunization

An alloantibody is an antibody produced to an antigen that an individual lacks [8]. Alloimmunization (alloantibody formation) is a known complication of transfusion and transplant therapy. Alloantibodies to cellular antigens can also be formed naturally during pregnancy and can put subsequent pregnancies at risk (see Chapter 23). Studies have demonstrated that the risk of alloimmunization is dependent on a

number of factors including the number of red cell containing units administered, the health of the recipient, and recipient genetic factors [17, 18]. Once an alloantibody has been generated, recipients may be at risk for future platelet refractoriness and transfusion reactions, described above.

Historically, the formation of an anti-D alloantibody has been considered the most concerning. D-antigens are highly immunogenic and anti-D antibodies can cause severe and potentially fatal hemolytic reactions. In the 1970s, it was demonstrated that 80% of healthy male volunteers formed an anti-D antibody when exposed to small doses of Rh-positive red blood cells [19]. The majority of hospitalized patients receiving red blood cell transfusions, however, are not "healthy." Subsequent studies have demonstrated a much lower rate of alloimmunization, ranging 20–30% in non-immunosuppressed individuals and massively transfused recipients [20, 21]. Alloimmunization rates of less than 10% were identified in immunosuppressed patients, including those with hematologic malignancies, acquired immunodeficiency syndrome (AIDS), or on immunosuppressive therapy [17, 22]. Decreased rates of alloantibody formation may be secondary to dampened responses to foreign antigens encountered in these states [9, 23].

Platelets differ from RBCs in that they express HPA antigens, in addition to ABO and Class I HLA antigens. Exposure to foreign HLA and HPA antigens can lead to the generation of HLA and HPA antibodies. Class I HLA antigens are the most immunogenic platelet antigens. Of acute myelogenous leukemia patients transfused with platelets, 45% formed HLA antibodies [9]. Conversely, only 8% of recipients demonstrated HPA antibodies following platelet transfusions [9]. Both types of antibodies can cause rapid clearance of transfused platelets, decreasing or eliminating their therapeutic benefit. Some of these platelet antibodies are capable of crossing the placenta, leading to neonatal alloimmune thrombocytopenia (NAIT). Platelet units may also contain variably small quantities of suspended RBCs. Rarely, passively transfused RhD-positive RBCs can cause anti-D antibody formation in RhD-negative individuals at a rate of less than 4% [24].

Chronically transfused patients pose a unique and difficult challenge to a transfusion service when considering alloimmunization risk. Treatment of patients with both benign and malignant hematologic diagnoses may require frequent red blood cell or platelet transfusions, but repeated exposure to foreign red cell and platelet antigens may result in the formation of multiple red cell, HLA, and/or HPA alloantibodies. Beyond the aforementioned complications of alloimmunization, finding compatible units for these patients may be difficult, leading to transfusion delays [9]. In these cases, providers must be aware that anywhere from hours to weeks may be required to obtain compatible RBC or platelet units. In some instances, nationwide donor searches are required.

Inventory Management

Since 2010, the National Blood Collection and Utilization Survey has noted a decrease in both blood donations and usage [25]. Modern blood banking practice has evolved to do more with less, challenging historical concepts of unit selection.

RBC Considerations

As our knowledge of alloimmunization and associated transfusion reactions has increased, demand for the least immunogenic blood products has increased. Universal RBC donor units were once identified as group O, RhD-negative (O-negative), but demands for this product have begun to outstrip availability [26]. In emergent situations requiring massive transfusion or large volume hemorrhage where the patient's blood type is unknown, O-negative product is the preferred standard for initial resuscitation to reduce the risk of RhD-alloimmunization and likelihood of an anti-RhD hemolytic transfusion reaction. Additionally, O-negative RBCs are almost exclusively used in neonates secondary to typing, sampling, and name challenges; those with significant alloimmunization; and in patients undergoing bone marrow transplant [26, 27]. Donor centers actively recruit group O donors, but D-negative individuals make up only 15% of the Caucasian and 8% of the Black populations [1]. In 2014, only 8.2% of American blood donors were O-negative [28]. These numbers highlight the scarcity and finite availability of O-negative RBC units.

To balance high demands with decreasing supply, blood conservation strategies and blood management programs are being instituted across the United States. Blood management programs are recommended by many professional societies and improve transfusion practices via evidence-based guidelines [29, 30]. Implemented programs may include written policies and procedures to prevent unnecessary transfusions via restrictive RBC transfusion recommendations (hemoglobin of <7.0 g/dL), lab-guided emergency transfusion protocols, or single unit orders with required interim RBC counts in the absence of a life-threatening bleed [24, 26, 31]. These strategies have been shown to reduce product use by 40%, while reducing patient morbidity and mortality [31, 32].

Strategies specific to conservation of O-negative units include transfusing this resource only to proven O-negative patients, using patient-specific criteria to switch from O-negative to O-positive product, adhering to restrictive transfusion thresholds, and limiting blood unit wastage [20, 24, 26, 27] (Table 2.4). Inventory management is crucial for all patient types. Even in neonatal centers, where O-negative product is almost exclusively used, aliquots of the same RBC

Table 2.4 Transfusion threshold recommendations [52–54]

Product	Indication	Recommendation to transfuse
Packed red blood cell units[a]	Hospitalized, hemodynamically stable adult	<7 g/dL
	Orthopedic surgery Cardiac surgery Preexisting cardiovascular disease	<8 g/dL
Platelet units[b]	Hospitalized, hemodynamically stable adult	<10 x 10^9 cells/L
	Elective central venous catheter placement	<20 x 10^9 cells/L
	Diagnostic lumbar puncture or major elective nonneuroaxial surgery	<50 x 10^9 cells/L
Plasma (FFP) products	Trauma patients requiring massive transfusion	Suggested to give (no specific recommendations made)

[a]These recommendations do not apply to those with acute coronary syndromes or transfusion-dependent anemia

[b]No official recommendations have been made regarding transfusion thresholds for those with intracranial hemorrhage

unit can be used for multiple neonates. Additionally, during large trauma or emergent situations where ABO and RhD type are unavailable, many centers have protocolized the use of O-positive RBCs in men and women beyond childbearing age [26]. Delayed hemolytic reactions due to RhD-alloimmunization in these populations are extremely rare and pose limited risk to the patient [24, 26]. This approach reserves RhD-negative product for known RhD-negative individuals and young women of childbearing age without a known type, who would be at risk for potentially fatal HDFN during pregnancy if alloimmunized.

Individual patient factors can also be considered when allocating O-negative units. Even with young females, hospital policies may advocate for switching to O-positive products during large volume resuscitations given local inventory and the patient's likelihood of survival [24]. Additionally, intensive care units have been identified as a location where switching to O-positive RBCs may be beneficial in times of product shortage. These patients are less likely to be chronically transfused and may have shorter life spans, making RhD-alloimmunization less significant [26].

Platelet Considerations

Various inventory management strategies have been implemented to address platelet product shortages. Bacterial contamination in platelets is a significant concern due to their room temperature storage (see Chapter 3). Accordingly, platelet shelf life was restricted to five days until 2016, when the US Food and Drug Administration (FDA) provided guidance on improving platelet safety while extending apheresis platelet shelf life to seven days with the use of approved storage containers, pathogen reduction technologies (PRT), and appropriate bacterial detection protocols (see Pathogen Reduction Technologies section below) [33]. These new guidelines have led to improved platelet availability and decreased outdating wastage [34].

Efforts to encourage responsible transfusion practices have also helped with shortages. Platelet transfusion thresholds are generally well established and have resulted in decreased use over time, though variation exists between centers [35, 36]. Platelet doses necessary to maintain hemostasis are controversial. Prophylactic administration of low-dose platelets ($1.1x10^{11}$–$4.4x10^{11}$) had no effect on bleeding incidence when compared to more standard doses [37]. Based on this evidence, medical directors may routinely split apheresis-derived platelet units in certain clinical situations to better ration platelet inventory.

Plasma Considerations

Plasma products present a unique challenge to inventory management. The universal plasma donor is group AB, representing only 4% of the population [5]. Especially in the Level 1 Trauma Center setting, having immediately available thawed plasma for emergent resuscitation is a necessity. While AB plasma would be the optimal choice, many centers now provide group A plasma for initial resuscitation efforts secondary to inventory limitations. Despite the concern for potential acute hemolytic transfusion reactions between A plasma and non compatible B recipients, no increased mortality or ABO-related acute hemolytic transfusion reactions have been reported with this change [38]. These outcomes are partially attributed to 85% of the population being compatible (either group O or A recipients) [5]. Additionally, recipients of massive transfusions are likely receiving high volumes of group O RBCs, which would not be affected by the transfused group A plasma anti-B antibodies [38, 39]. Furthermore, anti-B antibodies may be neutralized by secreted antigens in incompatible group B individuals [38]. Group A plasma is a safe alternative to group AB plasma during initial massive resuscitation while preserving group AB plasma inventory for other deserving patients in the hospital [9, 14, 23, 39].

Ordering Practices

Surgical service blood ordering practices are critical to inventory management in the hospital-based setting. Orders including:

- **Type and Hold**: Recipient ABO and RhD determined without antibody testing.
- **Type and Screen**: Recipient ABO, RhD, and antibody identification performed. No crossmatch performed on specific units, but compatible blood is available in most situations.
- **Type and Crossmatch**: Recipient ABO, RhD, and antibody identification performed. Units are removed from inventory and crossmatched to the recipient for compatibility.

A type and crossmatch order results in units being removed from inventory and assigned to a specific patient. These units are therefore unavailable in an emergency or for another patient. Over ordering of crossmatched products can result in inventory shortages and outdating of products that go unused. To mitigate these issues, crossmatch-to-transfusion (C:T) ratios are monitored, and a ratio > 2.0 suggests excessive ordering of crossmatched blood [6]. Strategies to reduce this waste include policies for preferential ordering of type and screens and the development of a hospital-specific Maximum Surgical Blood Order Schedule for common procedures that sets the number of units to be designated based on the intervention.

By combining their knowledge of hospital usage patterns, component outdating, and distance from their supplier, each transfusion services must determine their blood supply needs. Inventory levels must meet routine daily needs, while maintaining enough product for emergency-related transfusion requirements [6]. In particular, maintaining an adequate supply of O-negative RBCs (universal donor) for emergency procedures and rapidly expiring platelets levels remain daily challenges. Specialty products (e.g., cytomegalovirus negative, HLA-matched platelets) and modified products (e.g., leukoreduced, irradiated) requirements also need to be considered in terms of demand and supplier availability for delivery.

Serologic Versus Computer Crossmatch

Crossmatching is required on any product containing ≥2 mL of RBCs [6]. Serologic crossmatch has traditionally been used to demonstrate ABO compatibility between a recipient and donor product unit. Following ABO and Rh determination, an antibody screen is completed on the intended recipient. A potentially compatible unit is then selected for transfusion by the blood bank staff. The recipient's plasma is mixed with a red blood cell suspension made from donor unit. This mixture can then be examined for evidence of red blood cell clumping, indicating incompatibility.

Alternatively, an electronic records review or "computer crossmatch" can be used for the selection and verification of ABO-compatible RBC or whole blood products if the intended recipient has no current or historical clinically significant antibodies [40]. If computer crossmatching is used, the system must be validated on-site to select only ABO-compatible products, recognize required donor and recipient data, verify correct data entry, and be capable of identifying and alerting the user to discrepancies between the unit label and confirmatory testing, as well as between donor and recipient ABO and Rh types [40]. Additionally, electronic crossmatching is not permitted if ABO typing discrepancies are present [41].

Advantages of the electronic crossmatch use include decreased sample volume requirements, decreased workload for the transfusion service, and improved blood inventory management [6].

Emerging Infections

Beyond inventory concerns, modern transfusion medicine practice is also focused on the management of infectious disease risk. Transfusion-transmitted infections were described by the AABB in 2009 as "agents that pose a real or theoretical threat to transfusion safety, but for which existing effective interventions are lacking" [42]. Currently, the most dangerous emerging infections are those that have asymptomatic infectious phases, making donor screening difficult [43]. Difficult screening strategies equate with increasing the risk of transmission. The emergence of new pathogens is unpredictable, but mathematical modeling predicts a new transfusion-transmissible infection will emerge every five years [44]. Commonly considered infections in transfusion medicine are described below.

Arboviruses

Mosquitoes transmit the majority of medically significant arboviruses. Symptomatology can range from asymptomatic to severely debilitating disease to lethal. These viruses are frequently initially asymptomatic, making donor screening difficult to impossible in the early stages of disease. Transfusion-transmission has been documented for multiple arboviruses including Dengue and Zika virus, both recognized as emerging infection risks to the blood supply [43]. Unlike the majority of arboviruses that are unable to develop sufficient viremia within human hosts, these viruses maintain their viremia allowing for mosquito infection and continued spread in urban locations [45].

Dengue virus usually produces a self-limiting flu-like illness that rarely develops into life-threatening hemorrhagic fever. It can be transmitted by mosquitoes, blood transfusion, or solid organ transplant. There is currently no vaccine or treatment for infection, but symptomatology is usually asymptomatic to mild, and has not been demonstrated to be significantly different from non infected controls [42, 44].