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Past, Present and Future of Transfusion Medicine

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Transfusion Medicine: Past

'*Study the past if you would define the future*'.

–Confucius

The field of transfusion medicine traces its roots to early preclinical and clinical research performed in the late 1700s–early 1800s. The first reported human-to-human transfusion was performed in London on 26 September 1818, by Dr. James Blundell, using bespoke equipment (Figure 1.1). An obstetrician, Blundell famously used blood transfusions to resuscitate a series of women with severe anaemia due to postpartum haemorrhage [1].

Modern transfusion medicine began in 1901 with Dr. Karl Landsteiner's discovery of the ABO blood group system (Figure 1.2). To this day, the ABO system remains the most important barrier to safe transfusion. Landsteiner was a brilliant Austrian physician-scientist. In 1900, he performed a set of experiments in which he combined human red blood cells and serum obtained from different people in his laboratory. In one of history's greatest footnotes, Landsteiner wrote, 'the sera of healthy humans has an agglutinating effect, not only upon animal blood cells, but frequently upon blood cells from other individuals as well …'. [2]. This work led directly to the discovery of the ABO blood group system and laid the foundation for the routine, safe transfusion of red blood cells. In 1930, Landsteiner was awarded the Nobel Prize for his discovery.

In subsequent decades, many milestones followed, including the discovery of myriad blood group systems, the establishment of blood compatibility testing, the introduction of blood component technology, the use of plasma and whole blood during military conflicts, the development of Rh immune globulin (RhIg), the invention of apheresis technology, the discovery of transfusion-transmitted pathogens such as hepatitis B and C viruses and the implementation of donor infectious disease screening.

And then there was the human immunodeficiency virus (HIV) epidemic. It is difficult for transfusion medicine specialists entering the field today to imagine what hospitals were like in the late 1980s. Wards were filled with patients suffering from acquired immunodeficiency syndrome (AIDS), which at the time represented a uniformly fatal diagnosis. There was a point in

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Figure 1.1 Dr. James Blundell performing a transfusion using his Gravitator apparatus. *Source:* Blundell (1829) / Joseph Onwhyn / Public domain.

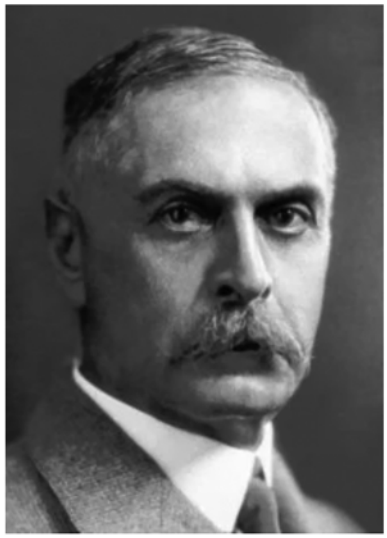

Figure 1.2 Dr. Karl Landsteiner, discoverer of the ABO blood group system. *Source:* Nobel Prize Outreach / Public domain.

the 1980s when transfusion recipients in some US regions had a greater than 1% per-unit risk of being infected with HIV. With current donor screening methods, that risk is now several orders of magnitude lower (Figure 1.3) [3]. The regulatory frameworks developed during the HIV years have persisted and grown, and blood collectors and hospital transfusion services are today among the most regulated areas in medicine.

Transfusion Medicine: Present

> '*Past is dead, future is uncertain, all you have is the present. So eat, drink, and be merry*'.
>
> –Albert Einstein

Transfusion Immunology

In some respects, red blood cell transfusions are like allogeneic transplants. Transfusion recipients are exposed to foreign antigens expressed on the transfused cells. Certain red blood cell antigens can trigger alloantibody formation in recipients, and this can lead to acute or delayed haemolytic transfusion reactions. There are no specific treatments for haemolytic reactions. Instead, transfusion services focus on preventing haemolytic reactions by providing immunologically compatible red blood cells. For transfusion medicine specialists, a solid understanding of the immunobiology of antibody formation is essential, as is a familiarity with the specific red

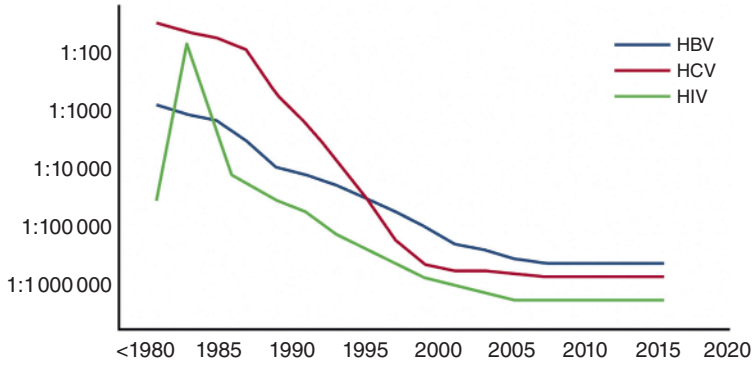

Figure 1.3 Per-unit risks over time of transfusion-transmitted hepatitis B virus, hepatitis C virus, and HIV. *Source:* Busch et al. [3] / with Permission of American Society of Hematology.

blood cell antigen–antibody systems responsible for haemolytic reactions. Similar immunologic concepts apply to components other than red blood cell units. Transfused platelets, for example, can be rapidly cleared from the circulation by recipient antibodies targeting human leukocyte antigen (HLA) molecules on the platelet surface. Indeed, suspected immune refractoriness to platelet transfusion is a common reason for transfusion medicine consultation.

First Principles

Relatively young as medical specialties go, transfusion medicine evolved as a merger of two different disciplines in medicine. Blood banking – everything to do with collecting, testing, storing and issuing blood products – developed within laboratory medicine, a branch of pathology. In parallel, medical practices aimed at optimising the use of blood products to treat patients developed within the subspecialty of haematology. Combine the laboratory-based and clinical aspects of blood transfusion, and you get transfusion medicine.

At its core, transfusion medicine is an evidence-based discipline. This means that clinical transfusion practices are ideally based not on lore, nor tradition, nor 'common sense', but on empiric, scientific data. That said, there are inevitably limits to the data, and clinical judgement is critical when treating an individual patient, whether considering transfusion or any other therapy. An essential section of this book reviews the types of studies used to gather evidence to support or refute clinical transfusion practices. Other important, practical considerations are discussed as well, e.g. blood availability and cost-effectiveness.

Owing to its origins in the clinical laboratory, transfusion medicine is firmly grounded in concepts of quality control, quality assurance and quality improvement in a way that other medical specialties are not. These principles inform all aspects of the daily practice of transfusion medicine, both inside and outside of the transfusion service laboratory. Blood transfusion is an inherently risky undertaking, yet the rates of severe adverse events, e.g. transfusion-related fatalities, are remarkably low. This is not an accident. Transfusion medicine shares many concepts and practices with other high-risk but 'super safe' industries, such as airlines. Transfusion medicine practitioners seek to rigorously define risks to patients and to drive those risks down as low as possible.

Transfusion medicine specialists face many challenging questions related to blood donation and collection. Among them: How do we get people to donate blood? How do we decide which potential donors are low risk and which are high risk for transmitting an infection to a recipient? How do we

balance the need for blood products to be safe with the need for collecting enough blood to meet society's needs? How do we ensure the rights, convenience and safety of people who wish to donate blood? How these and other rather complex questions are addressed varies around the world and continues to evolve.

Patient Blood Management (PBM) describes a constellation of approaches aimed at improving patient outcomes by reducing blood loss, optimising the patient's own red cell mass and limiting the use of transfusions [4, 5]. Many blood-sparing approaches that fall under the PBM paradigm can be traced back to efforts to support Jehovah's Witness patients who refused transfusion for religious reasons. As successful outcomes in this population were achieved without the use of transfusion, it was natural to ask why blood avoidance strategies could not be applied to all patients. These strategies include pre-operative measures, such as treating iron deficiency anaemia with iron supplementation, using cell salvage technology intraoperatively, paying meticulous attention to surgical haemostasis and tolerating a reasonable degree of anaemia post-operatively.

Many countries have instituted haemovigilance programmes to track adverse outcomes from transfusions (and near-misses) on a population level, aiming to identify and address important risks to patients. While transfusion-transmitted disease risks remain an important component of haemovigilance, the success of donor screening in mitigating infectious risks has in recent years prompted attention to shift to transfusion risks that extend well beyond 'what's in the bag'. Errors such as transfusing a unit of blood to the wrong patient can be fatal. Haemovigilance programmes, epitomised by the United Kingdom's Serious Hazards of Transfusion (SHOT) programme, have helped shine a spotlight on preventable errors (Figure 1.4), prompting many institutions to invest in robust safety technology, e.g. bedside bar code scanning at the critical times of blood bank sample collection and blood transfusion [6, 7].

Blood is an essential medicine, and ensuring the availability of transfusion support is a key consideration whenever emergency preparedness plans are formulated. Individual clinicians typically

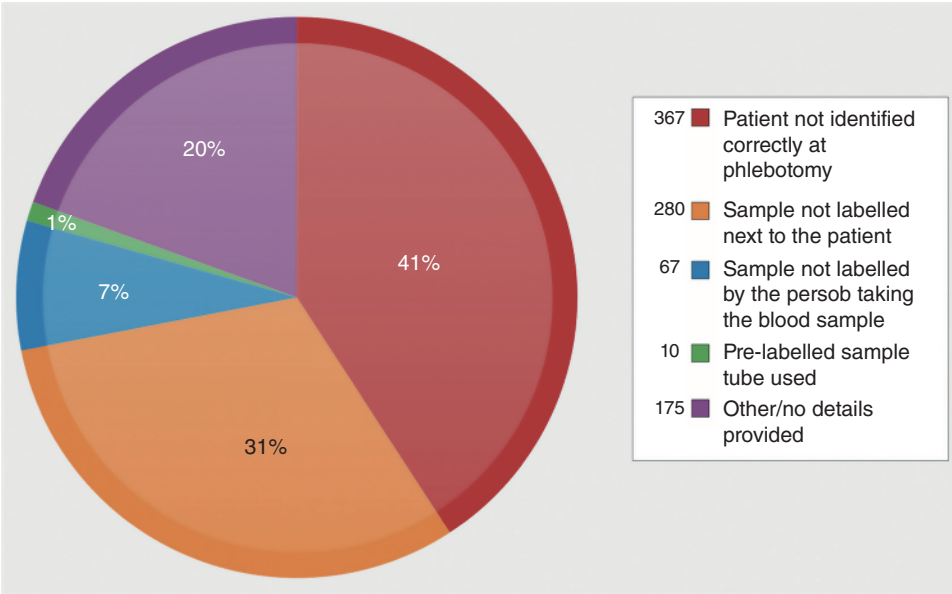

Figure 1.4 Causes of wrong blood in tube (WBIT) events in the UK. (Blood sample in tube does not match the identifiers on the label; these errors can lead to patients being transfused with the wrong unit.) *Source:* SHOT.

make transfusion decisions on individual patients in front of them, and transfusion medicine specialists often consult on individual patients who are challenging to transfuse. But the domain of responsibility for transfusion medicine extends far beyond the bedside of any one patient. Transfusion medicine specialists support a vital public health resource, and the critical need for blood services becomes strikingly evident anytime disaster planning is discussed.

Building Safe Systems

At each donation, blood donors are screened for infectious disease markers using a battery of assays that are among the most sensitive and specific in medicine. This approach has been incredibly successful. For many years, the risks of transfusion-transmission of, e.g. hepatitis B, hepatitis C and HIV have been so low that they cannot be measured directly. Instead, mathematical models are used to provide per-unit risk estimates of disease transmission. In high-income countries, those risks are below 1 per million units transfused.

Fundamentally, in performing pretransfusion serologic testing, either plasma with known antibodies is added to unknown cells, or unknown plasma is added to known cells and the presence or absence of cell agglutination provides the readout. While serologic testing today is often performed by automated instruments, some of the same manual serologic assays employed in the 1950s are still in use. Why have these old-fashioned methods persisted for so long? It is because they work. They are predictive in a way that many medical tests are not. If a patient has a negative antibody screen and a compatible crossmatch, we can be highly confident that transfused red blood cells will survive normally in the patient's circulation.

Usually, local responsibility for hospital transfusion services falls on the transfusion committee, a multidisciplinary group charged with ensuring the safe and appropriate use of blood products. There are many tools available to help support appropriate use of blood products, including evidence-based transfusion guidelines, electronic decision support, audit and feedback of transfusion practices and electronic positive patient identification systems [8].

A Lifesaving Therapy – in the Right Circumstances

Over the past two decades, medical approaches developed by militaries around the world have strongly influenced how actively bleeding patients are treated in civilian settings. During the twenty-first-century Iraq and Afghanistan conflicts, military providers began using plasma, platelets and red blood cell units in a '1:1:1' ratio to approximate the administration of whole blood and provide a 'balanced' resuscitation to patients requiring massive transfusion [9]. This practice was found to help prevent third-spacing of fluids (common following crystalloid administration) and was thought to help prevent dilutional coagulopathy. This approach to transfusion support is believed to have contributed to the improved survival of injured combat soldiers. Many other improvements in care were implemented at the time (better use of tourniquets in the field, faster transport to surgical facilities, the use of 'damage control resuscitation' and improved surgical techniques), so the precise contribution of the '1:1:1' approach to better clinical outcomes remains uncertain. Regardless, this approach was rapidly adopted in civilian medicine.

A return to whole blood transfusion was begun in the military realm and has gradually been gaining popularity in the civilian setting. It is particularly appealing for the prehospital setting, where administering one bag of whole blood is more practical, for instance, while flying an injured patient on a helicopter. Randomised controlled trials (RCTs) of whole blood versus components are now being conducted, as are studies of cold-stored versus room temperature-stored platelets.

A singular feature of transfusion medicine today is the focus on evidence from RCTs to help guide clinical transfusion practice. The 1999 Transfusion Requirements in Critical Care (TRICC) study [10] helped launch the RCT era in transfusion medicine. TRICC challenged the dogma at the time of transfusing patients to maintain their haemoglobin and haematocrit levels above 10 g/dL and 30%, respectively. In TRICC, and in most, though not all, of the many similar RCTs that followed, a restrictive red blood cell transfusion threshold was found not to confer worse patient outcomes than a liberal transfusion strategy [11]. Everything else being equal, transfusing less blood is appealing as it provides a lower risk of transfusion reactions, helps preserves limited blood resources and saves money. In some clinical settings, e.g. acute myocardial infarction, the available RCT data have not led to a consensus approach just yet [12, 13]. RCTs continue to inform practices involving the other 'classical' blood components (platelets [14], plasma and cryoprecipitate) as well as blood derivatives such as RhIg, used to prevent haemolytic disease of the fetus and newborn (Figure 1.5). Clinical trial data has likewise proved invaluable in guiding the use of therapeutic apheresis, an often-potent but often-misunderstood therapy that falls within the scope of transfusion medicine practice [15].

What Could Go Wrong?

Attend any lecture on transfusion-transmitted disease, and there is a good chance that a speaker will comment that 'blood is safer than it has ever been'. It is true. In the 1960s, it was simply accepted that about half of patients going for heart surgery would be infected with hepatitis following blood transfusion. A newly minted transfusion medicine specialist entering the field today can reasonably expect to see zero cases of transfusion-transmitted hepatitis over the course of their career, something that would be unimaginable in the past. Yet like any medical therapy, blood

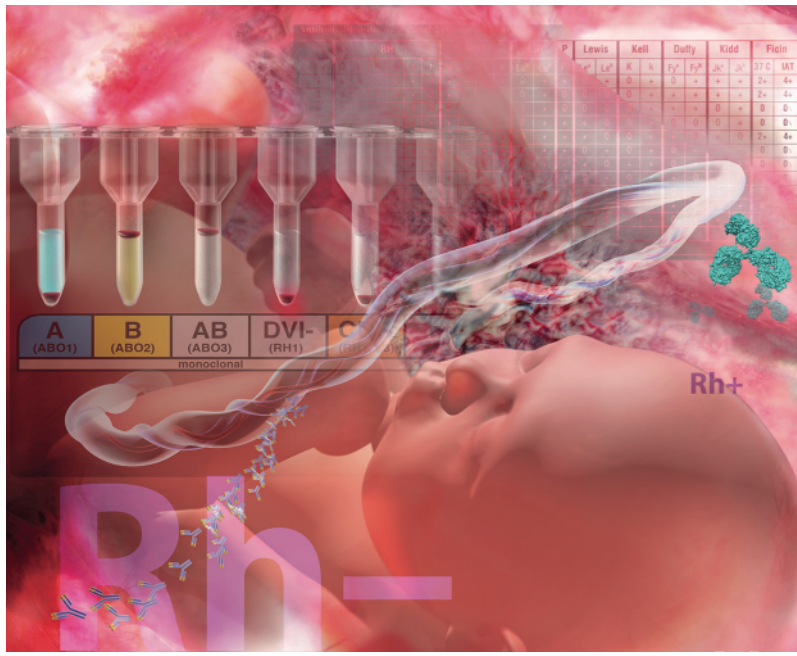

Figure 1.5 Transfusion services play an essential role in helping to prevent haemolytic disease of the fetus and newborn (HDFN). *Source:* © Linda Nye (2020) / Linda Nye.

has risks and benefits. It is likely that transfusion practices will continue to become marginally safer over time, but transfusion will never be completely safe. Today's risks of transfusion range in severity from harmless but annoying (e.g. febrile nonhaemolytic reactions and hives) to life-threatening (e.g. anaphylaxis and transfusion-related acute lung injury) [16].

Next-Generation Biotherapies

Why are blood products not managed as drugs and distributed by pharmacies? It is because they are alive. Unlike, e.g. antibiotics or antihypertensive medications, red blood cells and platelets are complex living cells that we use as medicine. If blood products were the original 'cellular therapies', then the second-generation of cellular therapies were bone marrow grafts, first harvested from marrow directly and later collected from peripheral blood using apheresis. In the past decade, use of the third generation of cellular therapies has exploded. These are genetically modified cells such as chimeric antigen receptor (CAR) T-cells used to treat cancer, and, increasingly, non-malignant diseases. Transfusion medicine specialists today frequently consult on transfusion issues that arise in the transplant setting, and they must keep up to date on the rapidly expanding family of cellular products being developed for clinical use.

Regulatory agencies and hospitals reasonably expect that the level of quality that is routinely established for all blood products should apply to all non-blood biologics (skin grafts and bone grafts). Transfusion medicine specialists are often asked to advise on how to manage tissues. Well-developed quality approaches used for blood products often translate well and help support the safe handling of tissues within healthcare facilities.

Transfusion Medicine: Future

'*It's tough to make predictions, especially about the future*'.

–Yogi Berra

Today, in high-income countries, the residual infectious disease risks of blood transfusion essentially come down to occasional bacterial contamination of platelets along with the very real possibility of some new pathogen entering the blood supply, akin to the HIV crisis of the 1980s. It is hoped that future improvements in pathogen reduction technologies will eliminate these risks while better preserving the function of blood products. It is also hoped that the function of current blood products, e.g. platelets for transfusion, can be improved in ways that will provide better patient outcomes. Novel approaches to blood product manufacturing, manipulation and storage are all being explored with goals such as making a more haemostatically effective platelet product. Concomitant efforts continue in trying to produce blood products *ex vivo* either through 'pharming' – growing cells in bioreactors – or by making truly artificial products, e.g. engineering lipid micelles and equipping them with molecules that provide oxygen-carrying or haemostatic functionality [17].

In terms of pretransfusion compatibility testing, it is unlikely that traditional serologic testing methodologies will disappear from transfusion service laboratories anytime soon. But as techniques such as next-generation DNA sequencing continue to grow in power, ease and affordability, it is likely that DNA-based approaches to matching patients with donor red blood cells will be more widely adopted over time (Figure 1.6) [18]. It is also expected that new drugs will sporadically pose challenges for compatibility testing, as happened with anti-CD38 and anti-CD47 monoclonals [19].

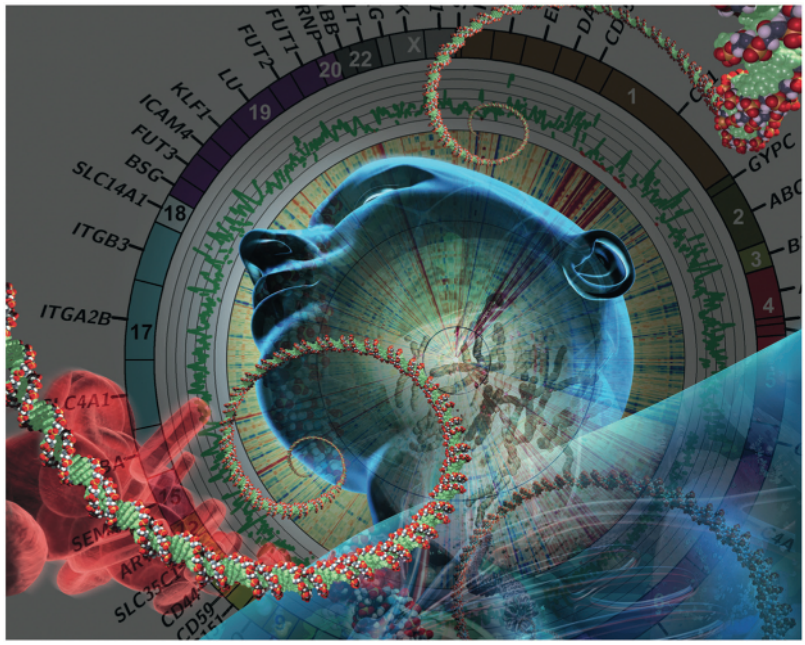

Figure 1.6 Artist's conception of red blood cell antigen prediction using whole exome sequencing. *Source:* © Linda Nye (2020) / Linda Nye.

Clinical transfusion practices will continue to be refined as more data become available from well-designed clinical trials [20]. It is also hoped that better *in vitro* assays will become available to help guide transfusion. Most red blood cell transfusion decisions are based on the patient's haemoglobin level, and most platelet transfusions are based on the platelet count. Assays that could provide useful information on tissue oxygenation or haemostatic function, respectively, have long been sought. Finally, the proliferation of new cell therapy approaches shows no sign of slowing. Well-established principles for the safe collection, manufacturing, testing, storage and use of conventional components will undoubtedly facilitate the development and safe deployment of novel cellular therapies moving forward.

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