

PRACTICAL TRANSFUSION MEDICINE

F I F T H E D I T I O N



EDITED BY
**MICHAEL F. MURPHY, DAVID J. ROBERTS
AND MARK H. YAZER**

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Practical Transfusion Medicine

Practical Transfusion Medicine

FIFTH EDITION

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Contents

List of Contributors *ix*

Preface *xv*

1 Introduction: Two Centuries of Progress in Transfusion Medicine *1*

Walter H. (Sunny) Dzik and Michael F. Murphy

Part I Basic Principles of Immunohaematology *11*

2 Essential Immunology for Transfusion Medicine *11*

Jaap Jan Zwaginga and S. Marieke van Ham

3 Human Blood Group Systems *20*

Geoff Daniels

4 Human Leucocyte Antigens *29*

Cristina V. Navarrete and Colin J. Brown

5 Platelet and Neutrophil Antigens *43*

Brian R. Curtis

6 Pretransfusion Testing and the Selection of Red Cell Products for Transfusion *58*

Mark H. Yazer and Meghan Delaney

Part II Complications of Transfusions *69*

7 Investigation of Acute Transfusion Reactions *69*

Kathryn E. Webert and Nancy M. Heddle

8 Haemolytic Transfusion Reactions *81*

Edwin J. Massey, Robertson D. Davenport and Richard M. Kaufman

9 Febrile and Allergic Transfusion Reactions *97*

Mark K. Fung and Nancy M. Heddle

- 10 Lung Injury and Pulmonary Oedema After Transfusion 108**
Steven H. Kleinman and Daryl J. Kor
- 11 Purported Adverse Effects of 'Old Blood' 118**
Lirong Qu and Darrell J. Triulzi
- 12 Transfusion-Induced Immunomodulation 125**
Amy E. Schmidt, Majed A. Refaai, Joanna M. Heal and Neil Blumberg
- 13 Transfusion-Associated Graft-Versus-Host Disease and Microchimerism 136**
Beth H. Shaz, Richard O. Francis and Christopher D. Hillyer
- 14 Posttransfusion Purpura 147**
Michael F. Murphy
- 15 Transfusion-Transmitted Infections 153**
Roger Y. Dodd and Susan L. Stramer
- 16 Bacterial Contamination 168**
Sandra Ramírez-Arcos and Mindy Goldman
- 17 Emerging Infections and Transfusion Safety 176**
Roger Y. Dodd

Part III Practice in Blood Centres and Hospitals 184

- 18 Regulatory Aspects of Blood Transfusion 184**
William G. Murphy, Louis M. Katz and Peter Flanagan
- 19 The Role of Haemovigilance in Transfusion Safety 193**
Katharine A. Downes and Barbee I. Whitaker
- 20 Donors and Blood Collection 203**
Marc Germain, Ellen McSweeney and William G. Murphy
- 21 Blood Donation Testing and the Safety of the Blood Supply 215**
Mindy Goldman
- 22 Production and Storage of Blood Components 222**
Marissa Li, Rebecca Cardigan, Stephen Thomas and Ralph Vassallo
- 23 Blood Transfusion in Hospitals 233**
Erica M. Wood, Mark H. Yazer and Michael F. Murphy
- 24 Blood Transfusion in a Global Context 254**
David J. Roberts, Alan D. Kitchen, Stephen P. Field, Imelda Bates, Jean Pierre Allain and Meghan Delaney

Part IV Clinical Transfusion Practice 264

- 25 Inherited and Acquired Coagulation Disorders 264**
Irina Chibisov and Franklin Bontempo
- 26 Massive Blood Loss 279**
John R. Hess
- 27 Blood Management in Acute Haemorrhage and Critical Care 287**
Gavin J. Murphy, Nicola Curry, Nishith N. Patel and Timothy S. Walsh
- 28 Point-of-Care Testing in Transfusion Medicine 302**
Matthew D. Neal and Louis H. Alarcon
- 29 Haematological Disease 312**
Lise J. Estcourt, Simon J. Stanworth and Michael F. Murphy
- 30 Blood Transfusion in the Management of Patients with Haemoglobinopathies 330**
Enrico M. Novelli
- 31 Heparin-Induced Thrombocytopenia 341**
Andreas Greinacher and Theodore E. Warkentin
- 32 Immunodeficiency and Immunoglobulin Therapy 357**
Siraj A. Misbah
- 33 Transfusing Neonates and Infants 371**
Ronald G. Strauss

Part V Patient Blood Management 383

- 34 Development of a Patient Blood Management Programme 383**
Jonathan H. Waters
- 35 Perioperative Patient Blood Management 393**
Martin Rooms, Ravishankar Rao Baikady and Toby Richards
- 36 Restrictive Transfusion Practice and How to Implement It 405**
Lawrence Tim Goodnough and Neil Shah
- 37 Using Data to Support Patient Blood Management 416**
Steven M. Frank and Jack O. Wasey

Part VI Cellular and Tissue Therapy and Organ Transplantation 429

- 38 Regulation and Accreditation in Cellular Therapy 429**
Zbigniew (Ziggy) M. Szczepiorkowski and Daniel Hollyman
- 39 Stem Cell Collection and Therapeutic Apheresis 442**
Khaled El-Ghariani and Zbigniew (Ziggy) M. Szczepiorkowski
- 40 Haemopoietic Stem Cell Processing and Storage 455**
Hira Mian, Ronan Foley and Pamela O'Hoski
- 41 Haematopoietic Stem Cell Transplantation 466**
Robert D. Danby, Rachel Protheroe and David J. Roberts
- 42 Cord Blood Transplantation 477**
Rachael Hough and Robert D. Danby
- 43 Recent Advances in Clinical Cellular Immunotherapy 490**
Mark W. Lowdell and Emma Morris
- 44 Tissue Banking 500**
Akila Chandrasekar, Paul Rooney and John N. Kearney

Part VII Development of the Evidence Base for Transfusion 508

- 45 Observational and Interventional Trials in Transfusion Medicine 508**
Alan T. Tinmouth, Dean Fergusson and Paul C. Hébert
- 46 Getting the Most Out of the Evidence for Transfusion Medicine 520**
Simon J. Stanworth, Susan J. Brunskill, Carolyn Dorée and Sally Hopewell
- 47 A Primer on Biostatistics 533**
Andrew W. Shih and Nancy M. Heddle
- 48 A Primer on Health Economics 549**
Seema Kacker and Aaron A. R. Tobian
- 49 Scanning the Future of Transfusion Medicine 560**
Jay E. Menitove, Paul M. Ness and Edward L. Snyder

Index 572

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Preface

The pace of change in transfusion medicine is relentless, with new scientific and technological developments and continuing efforts to improve clinical transfusion practice through patient blood management (PBM), which implores us to use the best available evidence when optimising pre-, peri- and post-operative management to reduce anaemia, prevent blood loss and reduce the need for transfusions. This fifth edition has become necessary because of rapid changes in transfusion medicine since the fourth edition was published in 2013.

The primary purpose of the fifth edition remains the same as the first: to provide a comprehensive guide to transfusion medicine. This book aims to include information in more depth than contained within handbooks of transfusion medicine and yet to present that information in a more concise and approachable manner than seen in more formal standard reference texts. The feedback we have received from reviews and colleagues is that these objectives continue to be achieved and that this book has a consistent style and format. We have again striven to maintain this in the fifth edition to provide a text that will be useful to the many clinical and scientific staff, both established practitioners and trainees, who are

involved in some aspect of transfusion medicine and require an accessible text.

We considered that this book had become big enough for its purpose, and the number of chapters has only been increased by one from 48 to 49. It is divided into seven sections that systematically take the reader through the principles of transfusion medicine, complications of transfusion, practice in blood centres and hospitals, clinical transfusion practice, PBM, cellular and tissue therapy and organ transplantation and development of the evidence base for transfusion. The final chapter on *Scanning the Future of Transfusion Medicine* has generated much interest, and it has been updated for this edition by three new authors.

We wish to continue to develop the content and to refresh the style of this book and are very pleased to welcome Professors David Roberts and Mark Yazer as co-editors. The authorship likewise has become more international with each successive edition to provide a broad perspective. We are very grateful to the colleagues who have contributed to this book at a time of continuing challenges and change. Once again, we acknowledge the enormous support we have received from our publishers, particularly James Schultz and Claire Bonnett.

1

Introduction: Two Centuries of Progress in Transfusion Medicine

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'States of the body really requiring the infusion of blood into the veins are probably rare; yet we sometimes meet with cases in which the patient must die unless such operation can be performed.' So begins James Blundell's 'Observations on transfusion of blood' published in *The Lancet*, marking the origins of transfusion medicine as a clinical discipline. Blundell (Figure 1.1) was a prominent London obstetrician who witnessed peripartum haemorrhage and whose interest in transfusion had begun as early as 1817 during his medical education in Edinburgh. He established that transfusions should not be conducted across species barriers and noted that resuscitation from haemorrhage could be achieved using a volume of transfusion that was smaller than the estimated blood loss. Despite life-saving results in some patients, clinical experience with transfusion was restricted by lack of understanding of ABO blood groups – a barrier that would not be resolved for another century.

The Nobel Prize-winning work of Karl Landsteiner (Figure 1.2) established the primacy of ABO blood group compatibility and set the stage for safer transfusion practice. Twentieth-century transfusion was advanced by the leadership of many physicians, scientists and technologists and repeatedly incorporated new diagnostics (monoclonal antibodies, genomics)

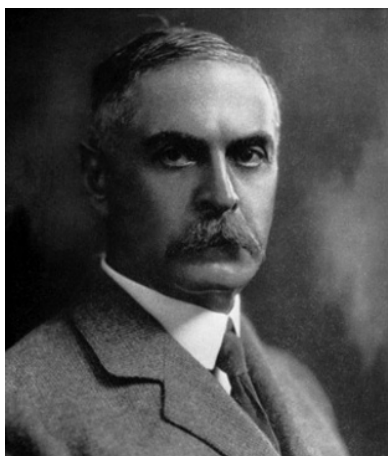
and new therapeutics (plasma fractionation, apheresis and recombinant proteins) to improve patient care.

Today, the field of transfusion medicine is composed of a diverse range of disciplines including the provision of a safe blood supply; the fields of haemostasis, immunology, transplantation and cellular engineering; apheresis technology; treatment using recombinant and plasma-derived plasma proteins; and the daily use of blood components in clinical medicine (Figure 1.3). Without transfusion resources, very little of modern surgery and medicine could be accomplished.

For decades, the challenge of transmitting new information in transfusion fell to Dr Patrick Mollison (Figure 1.4) whose textbook became the standard of its era. Mollison highlighted the importance of both laboratory practice (immunohaematology, haemostasis, complement biology) and clinical medicine in our field. *Practical Transfusion Medicine*, here in its fifth edition, seeks to build on that tradition and to give readers the foundation knowledge required to contribute both academically and clinically to our discipline. For readers about to enjoy the content of this book, the following provides a sampling of the topics presented within the text by leading experts in our field.



Figure 1.1 James Blundell.



K. Landsteiner

Figure 1.2 Karl Landsteiner.

Blood Donation Worldwide

Each year, approximately 100 million blood donations are made worldwide (Figure 1.5). A safe and adequate blood supply is now an

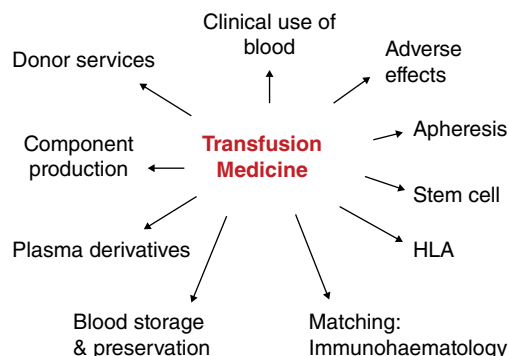


Figure 1.3 The range of transfusion medicine.



Figure 1.4 Patrick Mollison. Source: Garratty, Transfusion 2012;52:684–85. Reproduced with permission of John Wiley & Sons.

essential infrastructure requirement of any modern national healthcare system. The recruitment and retention of healthy blood donors is a vital activity of the field and the challenges and responsibilities faced by stewards of the blood supply are presented to readers in Chapters 18–22. Whilst the economically advantaged nations of the world have established all volunteer donor programmes with great success, data from the World Health Organization presented in Chapter 24 document that blood donation rates per capita in many low-income nations are insufficient to meet their needs. More research and investment is required so that all regions of the world can rely upon an adequate supply of safe blood.

Changing Landscape of Transfusion Risks

During the final two decades of the twentieth century, intense focus on screening blood donations for infectious diseases led to substantial

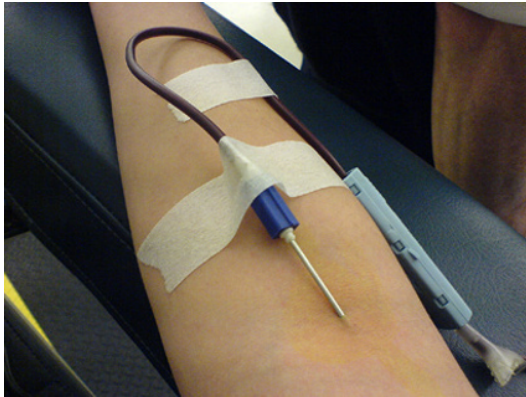


Figure 1.5 Blood donation.

progress in blood safety and a significant reduction in the risk of transfusion-transmitted diseases (Figure 1.6). Chapters 15–17 present an authoritative summary of this success. We currently enjoy a grace period when the risk of transfusion-transmitted infections is at an all-time low. However, progressive encroachment of humans upon the animal kingdom is expected to result in the emergence of new infections that cross species barriers. Haemovigilance, robust screening technologies and chemical pathogen inactivation are all being applied to address this concern and are reviewed within the text.

With the advent of the twenty-first century, the landscape of transfusion risk shifted its emphasis towards non-infectious hazards (Figure 1.7). Recent years have focused on improved understanding and prevention of transfusion-related acute lung injury, a topic covered in detail in Chapter 10. More recently, we have learned that circulatory overload from

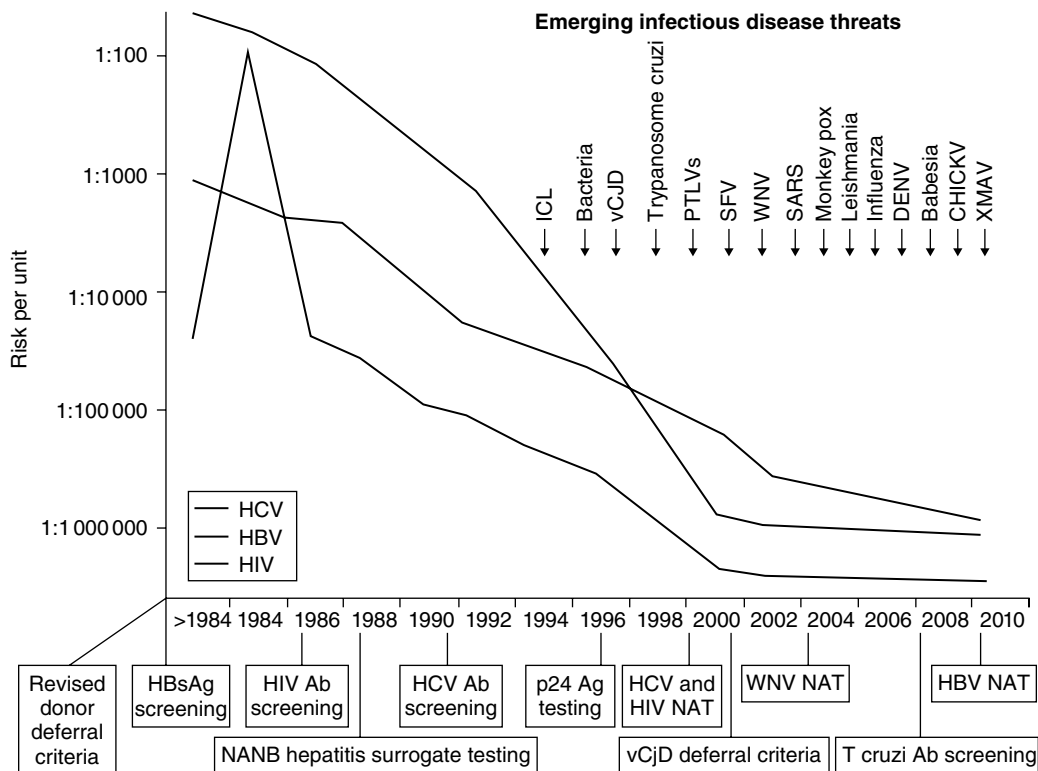


Figure 1.6 Risks of transfusion-transmitted infections over time.

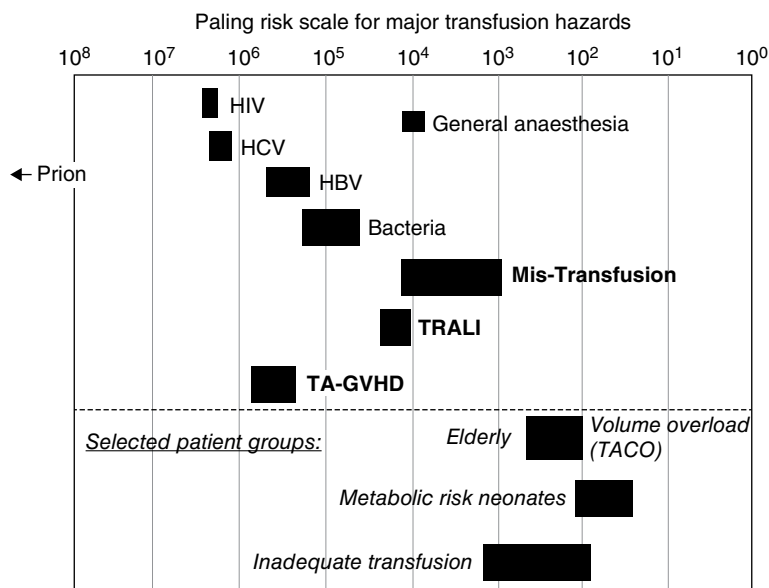


Figure 1.7 Paling scale of transfusion risk.

excessive transfusion is far more common than previously recognised. Yet Blundell himself specifically warned of it in his first description of transfusion: ‘to observe with attention the countenance of the patient, and to guard ... against an overcharge of the heart’ [1]. In addition, haemolytic reactions remain a serious hazard of transfusion. It is quite surprising that despite unimagined advances in internet connectivity, most nations still do not have a system for sharing patient blood group results or antibody profiles between hospitals, thereby failing to share information that would prevent acute and delayed reactions. Much can still be done to further reduce non-infectious hazards of transfusion. Readers will find that Chapters 7–17 provide state-of-the-art summaries of our current understanding regarding the full range of adverse effects and complications of transfusion.

Immunohaematology

Knowledge of the location and functional role of red cell surface proteins that display blood group epitopes has brought order out of what

was once a chaotic assembly of information in blood group serology (Figure 1.8). Readers will enjoy an up-to-date treatment of this topic in Chapters 2–6.

Today, red cell genomics has become a practical clinical tool and DNA diagnostics in immunohaematology extends far beyond the reach of erythrocyte blood groups. Genotyping has always been the preferred method for defining members of the human platelet antigen system and is well established for HLA genes in the field of histocompatibility (Figure 1.9). The clinical practice of transfusion medicine is now supported by DNA diagnostics targeting a wide range of genes, including those coding for complement proteins, human neutrophil antigens, haemoglobin polymorphisms and coagulation factors.

Despite advances in defining antigens, both clinical illness and blood group incompatibilities remain dominated by antibody responses of the patient. A robust form of antibody analysis and better control of the immune response remain important frontiers of our field. The ability to downregulate specific alloimmune responses would revolutionise the approach to

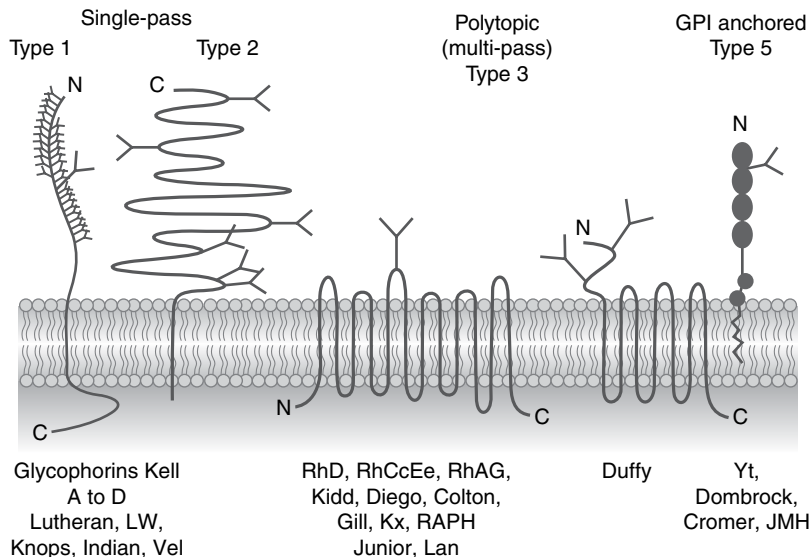


Figure 1.8 Red blood cell antigens. *Source:* Daniels G, Bromilow I. *Essential Guide to Blood Groups*, 3rd edn. Wiley: Chichester, 2014. Reproduced with permission of John Wiley & Sons.

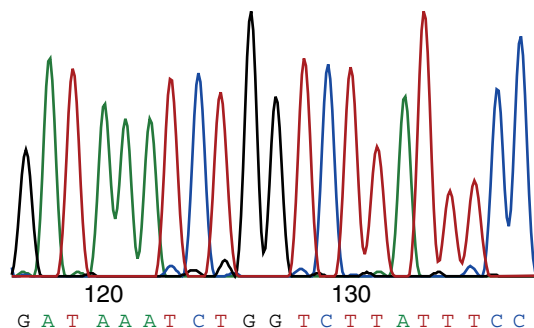


Figure 1.9 DNA sequence.

solid organ transplantation, haemophilia complicated by inhibitors, platelet refractoriness, red cell allosensitisation, haemolytic disease of the newborn and a host of other challenges that confront transfusion specialists every day.

In the meantime, we can offer patients powerful, yet nonspecific immune suppressants. And while the focus of many treatments is on reduction of pathological antibodies, it is increasingly clear that antibodies themselves do not injure tissues nearly as much as the complement proteins that antibodies attract.

Complement is at the centre of a wide variety of disorders, including drug-mediated haemolysis or thrombocytopenia, severe alloimmune or autoimmune haemolysis, cryoglobulinaemic vasculitis, HLA antibody-mediated platelet refractoriness and organ rejection, paroxysmal nocturnal haemoglobinuria, atypical haemolytic-uremic syndrome, hereditary angioedema, glomerulonephritis and age-related macular degeneration. With the development in the future of better agents to suppress complement, it can be anticipated that the focus of treatment may shift from removal of pathological antibodies to control of their effect.

Clinical Use of Blood Components: Evolution Based on Evidence

Recent years have witnessed a growing body of evidence derived from clinical research and focused on the proper use of blood components (Figure 1.10). While such research has lagged for plasma products, progress has been made

for both red cells and platelets. Ever since the landmark publication of the TRICC trial by Hebert and others [2], clinical investigators have repeatedly challenged the traditional 100 g/L haemoglobin threshold for red cell transfusion. There are now at least 11 well-designed, sufficiently powered randomised controlled trials documenting that a conservative haemoglobin threshold for red cell transfusion is as beneficial



Figure 1.10 RBC transfusion. Source: REX by Shutterstock. © Garo.

for patient outcomes as a more liberal threshold (Figure 1.11). These studies cut across a broad range of patient categories from infants to the elderly. As a result, in hospitals worldwide, red cell use is more conservative and transfusions are now withheld in nonbleeding patients until the haemoglobin concentration falls to 70 g/L. Looking ahead, we anticipate that future clinical research will seek to further refine the indication for red cells by addressing the fact that the haemoglobin concentration is but one dimension of tissue oxygenation and that the decision to transfuse red cells should include measures of both oxygen delivery and tissue oxygen consumption.

The last decade has also witnessed evidence-based refinements in the indication for platelet transfusion. The modern era of evidence begins with the work of Rebullia et al [3] who documented that a platelet threshold of $10 \times 10^9/L$ was equivalent to $20 \times 10^9/L$ for prophylactic platelet transfusions. Further advances came with the TRAP trial [4], demonstrating that reducing the number of leucocytes (and not the number of donors) was key to preventing HLA alloimmunisation, and the PLADO trial [5] which demonstrated that the traditional dose of platelets (approximately equivalent of that found in 4–6 units of whole blood) resulted in the same outcome as transfusion of three units or

Randomised trials of RCB transfusion threshold

Author	Name	Setting	Trigger	'n'
Hebert, 1999	TRIC	Adult ICU	7 vs 9	836
Kirpalami, 2006	PINT	Infants <1 kg	10 vs 12	457
Lacroix, 2007	---	Paediatric ICU	7 vs 9.5	637
Hajjar, 2010	TRAC	Cardiac surgery	8 vs 10	502
Cooper, 2011	CRIT	Acute MI (pilot)	8 vs 10	45
Carson, 2011	FOCUS	Hip surgery elderly	8 vs 10	2,016
Villaneuva, 2013	---	UGI bleed	7 vs 9	921
Walsh, 2013	RELIEVE	Older patients ICU	7 vs 9	100
Robertson, 2014	---	Traumatic brain	7 vs 10	200
Holst, 2014	TRISS	Septic shock	7 vs 9	998
Murphy, 2015	---	Cardiac surgery	7.5 vs 9	2,007

Figure 1.11 Trials examining the RBC transfusion threshold.

12 units as judged by the proportion of days with grade 2 or higher bleeding. Finally, the TOPPS trial [6] revealed that there was little value to prophylactic platelets among clinically stable patients undergoing autologous bone marrow transplantation. The goal now is to conduct more research on platelet transfusion outside the context of haematological malignancy. While we still have much more to do if we are to refine the clinical use of the traditional blood components, Chapters 34–37 on patient blood management and 45–46 in the section on developing the evidence base for transfusion should give readers a solid foundation upon which to improve clinical decisions regarding transfusion.

Urgent Transfusion

Care of the haemorrhaging patient has always been an essential aspect of transfusion practice. The tragedies of war and human conflict have repeatedly stimulated research focused on urgent transfusion during haemorrhage. Demand for knowledge in this area sadly continues and is amplified within violent societies by civilian trauma from firearms and in other societies by automobile injury. This is an area of changing practice patterns and readers will welcome the up-to-date focus found in Chapters 26 and 27. With the advent of increasingly complex surgery and deployment of life support systems such as extracorporeal membrane oxygenators, massive transfusion is no longer restricted to trauma. In fact, recent studies document that the majority of massive transfusion episodes are associated with surgical and medical conditions unrelated to trauma [7]. More research in these patient groups is needed.

Patients Requiring Chronic Transfusion Support

Chapters 29 and 30 address the needs of patients with haematological disorders who often require chronic transfusion support (Figure 1.12). Patients with haemoglobinopathies, thalassaemia,

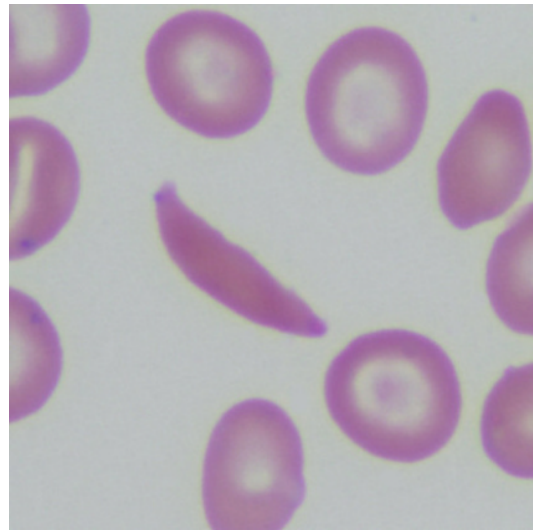


Figure 1.12 Sick cell anaemia.

myelodysplastic syndromes, aplastic anaemia, refractory anaemia, congenital and acquired haemolytic anaemia and those with chronic bleeding disorders such as hereditary haemorrhagic telangiectasia depend upon transfusion to sustain them. Worldwide, the numbers of individuals with severe uncorrectable anaemia is enormous. For these conditions, blood transfusion is seen at its raw, primal best: the sharing of blood from those in good health to those in need.

Obstetric, Neonatal and Paediatric Transfusion Medicine

Care of the low-birthweight, premature infant remains very challenging. Anaemia and thrombocytopenia result from physiology unique to these youngest of patients, as described in Chapter 33. Neonatal and paediatric transfusion medicine is filled with customary practices often based more on tradition than evidence. We applaud those who have conducted controlled trials that are summarised within the text, and look forward to additional clinical research designed to answer fundamental questions that confront the paediatric transfusion specialist.

Haemostasis and Transfusion

No area of transfusion medicine has seen such explosive recent innovation as the field of haemostasis. A wide range of anticoagulants is now available and the balance between anticoagulation, haemostasis and thrombophilia has become more complex. Transfusion therapy continues a long evolution from plasma replacement to the targeted use of a growing number of plasma-derived or recombinant products that influence haemostasis. Tools and treatments used in the past and then put aside, such as viscoelastic testing and antifibrinolytics, have made a strong resurgence and are finding new positions in the evaluation and treatment of bleeding. Additional haemostasis agents, which we will need to clinically master, are on the way. Chapters 25, 28 and 31 address these topics and will give readers new information on the important role of transfusion in the care of patients with disorders of haemostasis and thrombosis.



Figure 1.13 Cryopreservation in liquid nitrogen.

Cellular Therapies, Transplantation, Apheresis

Cellular therapy is a major growth area in transfusion medicine. The ability to mobilise haematopoietic progenitor cells, then harvest them safely in bulk numbers, process, freeze and successfully reinfuse them as a stem cell tissue transplant has completely revolutionised the field of bone marrow transplantation (Figure 1.13). Other therapeutic areas, such as treatment with harvested and manipulated dendritic cells, mesenchymal cells, T-cells and antigen-presenting cells, have progressed far more slowly. Nevertheless, with advances in gene engineering, the potential to treat illnesses with autologous reengineered cellular therapies is very bright. Chapters 38–44 present a detailed account of the current state of the art in cellular therapies as well as a glimpse of where this field is heading.

The Future

This fifth edition of this textbook concludes, as have previous editions, with reflections on the future of the field. While speculation on the future is never easy, our own view is that the ability to perform targeted gene editing is one of the most promising current research endeavours. CRISPR (clustered regularly interspaced short palindromic repeats) technology allows for the targeted excision of DNA at any known sequence (Figure 1.14).

Short tandem repeat DNA sequences (eventually renamed as CRISPR) were originally discovered as part of normal bacterial defence against viruses. Several genes in bacteria, called CRISPR-associated genes (cas), were found to code for nucleases specific for these repeat sequences, thereby disrupting viral genomes within bacteria. One of these cas genes, *Cas9*, was found to work efficiently within eukaryotic cells as a nuclease



Figure 1.14 CRISPR technology allows targeted excision of DNA. Source: Shutterstock. © GeK.

that could be guided by RNA to a specific DNA target. This RNA guide can be synthesised to match the cellular DNA area of choice. By delivering the *Cas9* nuclease and the guiding RNA into a cell, the genome of that cell can be disrupted or edited in a controlled manner.

One example of the application of CRISPR technology has focused on haemoglobin F production [8]. The *BCL11A* gene is the natural suppressor of haemoglobin F. *BCL11A* is turned on after birth, resulting in active downregulation of haemoglobin F transcription. CRISPR technology has been used to disrupt the promoter region of the *BCL11A* gene, thus removing its suppression with a resulting increase in haemoglobin F production. This approach has an obvious potential application in sickle cell disease where even a small increase in haemoglobin F expression can ameliorate

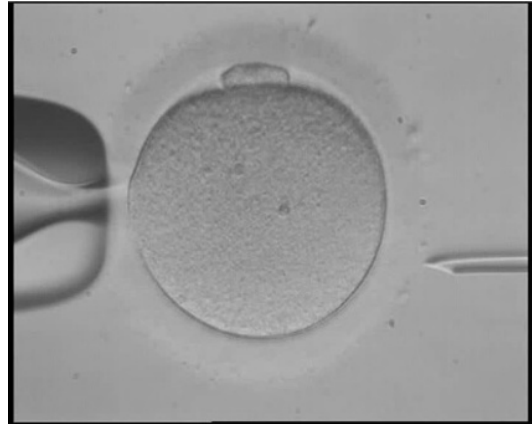


Figure 1.15 Cellular therapies of the future.

clinical symptoms. One can imagine the *ex vivo* manipulation of autologous CD34-positive cells using CRISPR technology followed by their transplantation into the sickle cell patient so as to produce a posttransplant phenotype with higher haemoglobin F expression (Figure 1.15).

Conclusion

James Blundell would immediately recognise a red cell transfusion if he saw one today. However, the great part of what we do would be incomprehensibly advanced and far beyond his understanding. In a similar way, the technologies of the future will revolutionise medical care in ways we can hardly imagine. Let us look forward to a time when we can reflect back on nonspecific immune suppression, apheresis therapy, blood group incompatibilities and one-dimensional laboratory triggers for transfusion care as practices that we needed to understand today so that we could achieve the promise of tomorrow.

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Essential Immunology for Transfusion Medicine

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Cellular Basis of the Immune Response

Leucocytes from the myeloid and lymphoid lineage form the different arms of the innate and adaptive immune system. Each cell type has its own unique functions.

Innate Immune Cells

Phagocytes and Antigen-Presenting Cells

Monocyte-derived macrophages, neutrophils (polymorphonuclear neutrophils, PMNs) and dendritic cells (DCs) function as phagocytes that remove dead cells and cell debris or immune complexes. In addition, these cells act as the first line of innate defence, ingesting and clearing pathogens. The first step is recognition of pathogen-derived signals (pathogen associated molecular patterns, PAMPs) or danger-derived signals from inflamed tissues (danger-associated molecular patterns, DAMPs) via pattern recognition receptors (PRR). This triggers their differentiation and expression and/or secretion of signalling proteins. Some of these proteins (such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)) increase acute-phase proteins that activate complement, while others (chemokines) attract circulating immune cells to the site of infection. DCs and macrophages

also serve as antigen-presenting cells (APCs) that present digested proteins as antigen to specific T-cells of the lymphoid lineage. PRR ligation in this setting induces maturation of APCs with the acquisition of chemokine receptors, which allows their migration to the lymph nodes where the resting T-cells reside. Simultaneously, mature APCs acquire co-stimulatory molecules and secrete cytokines. All are needed for T-cell activation and differentiation and eventually the immune response to the specific pathogen. The type of PRR ligation determines the production of cytokines, which in turn induces the optimal pathogen class-specific immune response.

Adaptive Immune Cells

T-Lymphocytes

After migration of progenitor T-cells to the thymus epithelium, billions of T-cells are formed with billions of antigen receptor variants. Each lymphocyte expresses only one kind of heterodimeric T-cell receptor (TCR). Immature T-cells initially express a TCR receptor in complex with CD4 and CD8 molecules, which respectively interact with major histocompatibility complex (MHC) class II and class I molecules. The presentation of self-antigens within such MHC molecules on thymic stromal cells determines the fate of the immature T-cells.

First of all, these interactions induce T-cells that express only CD4 or CD8. Most important, however, is that these interactions are responsible for the removal of T-cells that have a TCR with high binding affinity for a self-antigen MHC complex. The cells that survive this so-called 'negative selection' process migrate to the secondary lymphoid organs. There, TCR-specific binding to complexes of MHC can activate them with non-self (e.g. pathogen-derived) antigens on matured APCs. Interactions between the co-stimulatory molecules CD80 and CD86 on the APC with CD28 on the T-cell subsequently drive the activated T-cells into proliferation. Without this co-stimulation (e.g. by not fully differentiated APCs or by insufficient or absent PRR ligation), T-cells become nonfunctional (anergised). The requirement of PRR-induced danger signals thus forms a second checkpoint of T-cell activation to prevent reactivity to self-antigens. Hence, the normal removal of autologous apoptotic or dead cells and cell debris by phagocytes will not lead to alloimmunization.

While immunoglobulins bind to amino acids in the context of the tertiary structure of the antigen, the TCR recognises amino acids on small digested antigen fragments in the context of an MHC molecule. MHC characteristics ensure near endless protein/antigen binding capacities and thus adaptation of the immune response to new/rapidly evolving pathogens. MHC class I is expressed on all nucleated cells and presents so-called 'endogenous' antigen-constituting self-antigens, but also antigens from viruses and other pathogens that use the replication machinery of eukaryotic cells for their propagation. Viruses and parasites (like *Plasmodium falciparum*) can hide in red blood cells because the latter lack MHC but fortunately red cells also lack the DNA replication machinery for such pathogens.

MHC class II molecules of APCs present antigenic proteins that are ingested or endocytosed from the extracellular milieu. The described antigen expression routes, however, are not absolute. Specialised DCs in this respect can also express pathogen-derived proteins that have been taken up by the DCs via the endocytic

route and other extracellular-derived proteins on MHC class I to CD8+ cytotoxic T-lymphocytes (CTLs). Conversely, cytosolic proteins can become localised in the endocytic system via the process of autophagy and become expressed in MHC class II.

Paradoxically, the fact that T-cells become activated only when the specific TCR recognises alloantigens in the context of its own MHC (termed MHC restriction) seems to refute the condition whereby MHC/HLA mismatched tissue transplants are rejected. Many acceptor T-cells, however, can be activated only by a donor-specific MHC; an additional alloantigen is not needed for this. A large circulating pool of T-cells reacting with non-self MHC is usually present and explains the acute CD8-dependent rejection of non-self MHC in transplant rejection that occurs without previous immunisation.

T Helper (Th) Cells

Differentiation into Th cells is dependent on cytokines and/or plasma membrane molecules derived from the APC. Different Th subsets can be characterised by their cytokine release and their action in infected tissues. Th1 cells that release interferon (IFN)-gamma and IL-2 aid macrophages to kill intracellular pathogens upon cognate (i.e. antigen-specific) recognition of the macrophage. In addition, Th1 cells support CTL function and are required for optimal CTL memory formation. Th17 cells releasing IL-17 and IL-6 probably enhance the early innate response by activating granulocytes and seem most needed for antifungal immunity. Both Th1 and Th17 cells are drivers of strong pro-inflammatory immune responses that also induce (partly) collateral tissue damage, which might explain their association with autoimmunity. Classically, Th2 cells support B-cell differentiation and the formation of antibodies. These IL-4, -5 and -13 releasing Th2 cells, furthermore, help to kill parasites by inducing IgE production, which activates mast cells, basophils and eosinophils.

The recently defined follicular T helper cells (Tfh) have now been recognised as the main CD4 T-cell subset that supports induction and