Practical Transfusion Medicine
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Preface to the Fourth Edition

The pace of change in transfusion medicine is relentless with new scientific and technological developments, and continuing efforts to improve clinical transfusion practice and avoid the use of blood wherever possible. This fourth edition has become necessary because of rapid changes in transfusion medicine since the third edition was published in 2009.

The primary aim of the fourth edition remains the same as the first, that is to provide a comprehensive guide to transfusion medicine. The book aims to include information in more depth than contained within handbooks of transfusion medicine and to present that information in a more concise and ‘user-friendly’ manner than standard reference texts. The feedback we receive from reviews and colleagues is that this objective continues to be achieved and that the book has a consistent style and format. We have again strived to maintain this in the fourth 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 the book had become big enough for its purpose, and the number of chapters has been reduced by one from 49 to 48. It is divided into seven sections, which systematically take the reader through the principles of transfusion medicine, the complications of transfusion, practice in blood centres and hospitals, clinical transfusion practice, alternatives to transfusion, cellular and tissue therapy and organ transplantation and the 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.

We wish to continue to develop the international readership and are very pleased to welcome Professor Nancy Heddle as a co-editor. 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 Jennifer Seward and Maria Khan.
Introduction: recent evolution of transfusion medicine

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Introduction to the introduction

‘May you live in interesting times’ (attributed to an ancient Chinese proverb).

This quotation, sometimes referred to as the Chinese curse, seems to be an appropriate statement to introduce the fourth edition of Practical Transfusion Medicine. Although it has been attributed to an unknown ancient Chinese proverb, its origin has not been determined, its attribution remains unclear and several of my Chinese colleagues suggest that it does not sound like a saying that emanated from China. One theory suggests that an original proverb translated to say ‘It’s better to be a dog in a peaceful time than be a man in a chaotic period’ may be the origin and additional Wikipedia information suggests sources from the American Society of International Law Proceedings in 1939, or attributions to Polish or Jewish roots.

Regardless of its source, this curse has become a blessing readily demonstrated by the growth of transfusion medicine as witnessed by the evolution of Practical Transfusion Medicine into this fourth edition. The transfusion medicine world has used transformational problems such as the HIV epidemic and growing concerns of patients and physicians about blood safety to address and anticipate transfusion-related problems. Physicians now seek evidence that our current and evolving practices are based upon a solid foundation. This current volume has evolved from its humble original purpose to provide transfusion medicine educational material for haematology trainees in the United Kingdom (the first edition in 2001 through subsequent editions in 2005 and 2009) to become a comprehensive text with a distinguished international cast of authors. Former editions of the text have described the developing and broadening field of transfusion medicine for a multidisciplinary group of primary transfusion medicine practitioners to an increasingly diverse group of clinicians and supporting personnel dependent upon our services. This fourth edition continues the documentation of this movement to enhance blood safety and evaluates a growing armamentarium of options for blood and cellular therapies, based upon a foundation of evidence that continues to look forward but also has looked backward to substantiate or refute practices of the past. The transitions documented in the past ten years of the book’s history have not always been easy or straightforward, but readers of the text will understand that the transfusion medicine community has addressed the challenges of the curse of ‘interesting times’ and turned them into enhanced patient care opportunities.

Modern transfusion therapy would not be possible without the discoveries of the heterogeneity of blood group antigens by pioneers such as Landsteiner, Levine and Wiener, the development of anticoagulant preservative solutions for red cells stimulated...
by military requirements, evolving blood separation and storage systems that have permitted collection of platelets and haemopoietic stem cells, and laboratory systems that permit matching of blood components from donors to recipients, after other laboratory systems have been utilized to maximize the likelihood that donor blood is free of transmissible pathogens. Much of this development has been documented in other venues. It is highly unlikely that any attempt that I might make to highlight these developments would add value to this introduction, so I will avoid any attempt to recapitulate this history so well documented in other transfusion texts.

Drs Michael Murphy and Derwood Pamphilon, now joined in this fourth edition by Nancy Heddle, have provided an excellent matrix for this introduction, emphasizing the recent evolution of transfusion medicine by their selection of seven sections of transfusion medicine activity in the current text. Although I have only seen the outline of the carefully selected list of authors, I will attempt to highlight some of the areas that have evolved recently in the last ten years that will be fully discussed in the text. You will have to wait like me to see what is ultimately written in the book, but I have no doubt that you and I will enjoy and benefit from this fourth edition of Practical Transfusion Medicine.

**Basic principles of immunohaematology**

In the lifetime of this book, there has been an explosion of development in molecular testing of blood groups on red cells and other blood and cellular components that are beginning to be applied in donor screening and pretransfusion testing. Although the serological tests that are used to identify blood donor antigens and recipient blood groups and antibodies are still widely applied in hospital and donor centre settings, the capability of these testing systems has been enhanced by automated methodology that reduces human testing errors and enhances turnaround time in transfusion services.

Many blood centres and transfusion services are starting to use molecular red cell antigen detection methods to screen blood donor inventories and to resolve difficult patient problems where recent transfusions, autoantibodies or complicated transfusion histories make these testing systems a valuable adjunct to routine methods. With these methodologies, blood centres have the capability of performing routine red cell phenotype analysis that could permit more specific donor–patient matching of transfusion therapies. While this capability has clear-cut advantages for problem patients, the value of moving to more comprehensive transfusion matching remains unproven. Similar systems may enhance platelet transfusion therapy as well. Although prospective matching has not been shown to reduce alloimmunization for red cells or platelets in the past, even for high risk patient groups, future studies are likely to continue to explore the utility of prospective matching; if shown to have value for patients, it can then be determined if the clinical advantages justify the costs of these developments. Enhanced antigen screening capability for cellular antigen systems such as HLA may prove to be particularly important for cellular therapies that are expected to grow rapidly in the future. Broader application to platelet therapies will probably be seen in coming years. Leucocyte reduction was shown to be important in reducing platelet alloimmunization by the trial to reduce alloimmunization to platelet (TRAP) study in the 1990s, but the problems of platelet alloimmunization and specific platelet donor matching have not vanished, remaining a persistent problem for referral centres treating alloimmunized patients.

As one who studied alloimmunization to red cells and other transfusion components in the past, it is encouraging that a number of investigators are applying immunological methods in animal systems to determine how the process of alloimmunization occurs and whether there are therapies that could be applied to prevent alloimmunization or reverse clinically significant alloantibodies in affected patients. Our future transfusion therapies may be enhanced by learning which patients are at risk for alloimmunization and the pathophysiological underpinnings of alloimmunization as they apply to transfusion therapy. Leucocyte reduction can reduce platelet alloimmunization, suggesting that more extensive reduction of white cells or white cell function via pathogen reduction systems could become critical components for transfusion therapy. Prevention or reversal of alloimmunization to HLA would enhance solid organ transplant programmes, where previously immunized recipients are currently denied transplant options or required to undergo dangerous and expensive treatments to permit an incompatible solid organ or
haemopoietic cell transplant. The growing capability to manoeuvre around previously impenetrable ABO barriers shown in the last ten years provides some encouragement that we will become equally successful in dealing with HLA barriers or xenotropic antigens that prevent transplants of solid organs from donor animals.

Our increased understanding of immunohaematological principles has improved our capability to reduce adverse transfusion complications. The past ten years featured the recognition and attack of TRALI, identifying and mitigating these reactions for some but not all blood recipients. Other persistent transfusion problems such as delayed haemolytic transfusion reactions, TRALI not caused by donor antibodies and allergic transfusion reactions should be amenable to detection and prevention by better use of our evolving knowledge of immunohaematology. It may also be possible to gain better quantification and understanding of the adverse effects due to immunomodulation, such that we can reduce this transfusion complication for patients.

Complications of transfusion

Having been the director of a large community blood centre and a major academic transfusion service during the chaotic era of HIV awareness and prevention from 1980 onward, it is refreshing that the overwhelming concerns about blood safety that affect patients and their physicians have lessened dramatically during the lifespan of this book. The HIV era followed by identification of HCV and its detection were clearly an episode of ‘life in interesting times’. When providing transfusion medicine education to medical students or clinical updates to practitioners nowadays, however, they seem unconcerned with the current risk of HIV from a blood transfusion, a topic that dominated our interactions ten years ago. Although this state of relief is apparent in the developed world, blood safety concerns still remain high in developing countries, where donor screening and testing capabilities are still being developed. In a similar vein, the media in developed countries still remains eager to find the next transfusion pestilence, as shown by our recent flirtation with XMRV and SARS. Over the past ten years, with little public recognition, we enhanced testing for HCV, identified and prevented a major epidemic of West Nile Virus infections from blood donors and made initial steps to reduce the risk of septic transfusions from platelets.

As we take pride in this collective record of accomplishment and recent track record in mitigating transfusion-transmitted infections, complacency is not an option; diligence towards reducing and eliminating transfusion risks must remain a primary transfusion medicine objective. In the United States, there is growing evidence that babesia transmission and dengue infection should remain high on a surveillance list of emerging concerns. These infections and how we address them will continue to raise conflicting points of view, however. Although we initiated routine screening for Chagas’ disease, the limited detection rates and minimal evidence of transmission from previously infected donors using lookback studies has led to modifications of testing algorithms. These steps were justified to reduce costs to the blood centres and hospitals, but test kit providers have lost expected revenue, which may lessen their enthusiasm to develop new testing methods for infections that are not widespread or remain geographically constrained. As new candidate pathogens are identified and we continue to investigate these potential transfusion threats in keeping with the precautionary principle, these recent events may limit our ability to respond rapidly without expensive studies and unrewarded investments by test providers. In many cases, our concern for blood safety and mitigating transfusion risks from emerging infections gets ahead of regulatory guidance, so that the process by which we prioritize our activities in the blood safety arena remains difficult in the developed world. In the developing world and perhaps with increased frequency in developed countries, these processes will be affected by cost constraints and concerns about cost effectiveness in an era where reimbursement concerns loom large. As a discipline, we have also been ineffective in getting input from clinicians who order blood about these evolving blood safety concerns.

A number of blood safety concerns could be reduced by adoption of pathogen reduction systems. There is widespread use of pathogen reduction for plasma fractions from donor pools and increased use in blood components such as platelets and plasma in Europe and other developed countries outside the USA. In the USA, licensure and adoption have been delayed by regulatory concerns about adverse reactions in
Clinical trials and the lack of significant emerging infections on the horizon that would make favourable risk/benefit calculations. Pathogen reduction for red cells is still under development and may be slow to achieve licensed status due to antibody development with early formulations. Even if licensure is achieved, adoption may be stymied by cost considerations if pathogen reduction is advantageous for disease transmission issues alone. If these systems can be shown to reduce or eliminate some donor loss through travel history exclusions or elimination of unnecessary tests, or demonstrate other advantages for patients such as reduction of alloimmunization or prevention of graft versus host disease, the case for adoption by transfusion services will be enhanced.

Although most sections of transfusion complications focus upon infectious problems, the remaining chapters of this section provide extensive discussions of noninfectious transfusion complications. Progress in reducing these often ignored transfusion complications has been enhanced by the stable state of transfusion infections and our attempts to document the occurrence of all adverse effects through haemovigilance systems which began in the UK and have now spread to other countries throughout the world. The UK Serious Hazards of Transfusion (SHOT) programme highlighted TRALI cases as an important issue in its early versions, prompting actions of donor screening, consensus building, case reporting and product manipulations, which have lowered the rates of these reactions. It is hoped that these systems will become more widespread, move towards active rather than passive reporting and provide prioritized problem lists for further blood safety activities. A recent review reminds us that ‘blood still kills’, so attacks on common adverse transfusion effects such as immunomodulation, bacterial sepsis and the persistent problems with haemolytic reactions will move higher on the action list of transfusion medicine. The recent past has featured more discussion and action on these persistent problems affecting transfusion recipients, and the discussions of the status of these issues in the fourth edition of Practical Transfusion Medicine will provide an update of recent progress and opportunities for improvement.

The chapters of this section will also provide perspective on another issue of growing importance, the controversial debate of whether older blood has deleterious effects on transfused patients that could potentially be reduced by using fresher red cells. The medical literature is replete with retrospective studies from surgical cohorts that purport to show that older blood is harmful. These studies have stimulated the appropriate response from our community to initiate prospective clinical trials now underway in cardiac surgery and intensive care unit patients to address these issues. Basic and applied research studies on red cell storage, an area where we may have been inappropriately complacent, have been funded and are being reported in the literature and lay press. Ongoing research will determine whether the suggested culprits of nitric oxide, microparticles, nontransferrin bound iron or other biologic modifiers can be manipulated by storage systems to reduce adverse effects for patients if the prospective trials prove that there is a problem with older blood.

Practice in blood centres and hospitals

This section of the text provides the background and status report for transfusion-related activities in hospitals and blood centres. The shifting breadth in the new edition highlights international activities more broadly than previous editions, which were more Europe focused. Although recent editions were strong and comprehensive, multiauthored chapters from international authorities will address the challenge of describing current systems throughout the world, with the goal of broadening the experience base of all readers. As examples, the UK-based hospital chapter is now written by authors from Australia, the USA and the UK, and regulatory aspects that emphasized UK issues now include the perspective of authors from the USA, Canada and New Zealand as well as the UK. Increased emphasis is placed upon the global context of transfusion.

One of the triumphs of the last ten years has been advances made in developing countries through local initiatives, stimulated and enhanced by support from developed countries. The US President’s Emergency Plan for AIDS Relief (PEPFAR) aided the development of national blood programmes in sub-Saharan Africa with funding by the CDC, which were implemented by experts from the USA including AABB and Europe from Sanquin. The National Institutes of Health in the US funded international epidemiological research programmes in Brazil and China through the Retrovirus
Epidemiology Donor Study (REDS) programme and other national blood service organizations provided financial support and expertise for blood programmes in the developing world. While the progress has been substantial, it remains an uphill climb to bring transfusion safety and an adequate supply of safe volunteer donor blood throughout the world, but we can take pride that we are collectively pursuing the challenge with documented results.

Although much of the text is aimed at educating clinicians about blood services, there have been major developments in blood centres and hospital transfusion services to apply standardized procedures to improve patient care. The activities in blood centres in the developed world to bring standardized blood components from a heterogeneous group of blood donors to enhance blood safety have reduced transfusion complications; the parallel development of quality-based laboratory systems for testing, storage and distribution of blood components to patients upon the request of an educated physician base has also addressed these objectives. The chapters in this section prove to be of more utility to committed transfusion medicine practitioners but will be helpful to clinicians who advise on transfusion programmes through medical staff committees and provide transfusion consultation and support to less knowledgeable clinical colleagues.

### Clinical transfusion practice

One of the positive outcomes from blood safety initiatives has been our response to regulatory pressures to standardize blood collection and preparation processes. Although there are clear benefits in terms of blood safety from standardized procedures, we have become increasingly aware that modifications in the components we transfuse are required to meet the unique needs of different patient populations. Neonatal and paediatric transfusions have required hospital transfusion services to modify their practices to administer effective therapies in reduced volumes to these patients. Fresher blood components may be required for subsets of these patients and blood components with reduced potassium loads for massively transfused children are more commonly provided. The availability of recombinant coagulation factors has revolutionized the care of haemophilia. In a similar manner, new factors such as VIIa have been introduced for broader patient groups with acute haemorrhage, raising concerns about efficacy, toxicity and costs for these agents. Reducing the plasma load in platelet recipients, a process initiated in Europe to save plasma for the production of fractionation products, is becoming more common as a means to reduce ABO haemolytic reactions or allergic transfusion reactions in platelet recipients who receive the platelets for haemostasis but do not really benefit from the accompanying plasma.

We have begun to recognize that our approaches to patients with massive blood loss require rethinking. Data from the military suggest that early resuscitation using large volumes of plasma can save lives, leading to the development of massive transfusion protocols in hospitals with red cells, plasma and platelets being administered in a 1:1:1 ratio. These practices are now being extended to other patients with major haemorrhage who clearly require red cell support, but the documentation that they would benefit from 1:1:1 support is not available. Meeting the needs of trauma patients, but avoiding overtransfusion for patients who might not benefit has become an ongoing challenge. At the same time, as frozen plasma use is increasing dramatically in trauma, we recognize that frozen plasma is our most inappropriately ordered blood component, commonly used to correct trivial elevations of coagulation tests or prevent bleeding in procedures where evolving evidence has shown no medical value from this risky transfusion intervention. Complicating these issues are the many problems with plasma administration: ABO antibodies that make products unavailable as a universal therapy, large volumes that put patients at risk when acute care is needed, slow processing times due to thawing requirements and inadequate potency for acute haemorrhage or reversal of anticoagulation.

These evolving medical transfusion issues suggest that the transfusion service may become more important as a source of product modifications, becoming more of a wet pharmacy for blood components. Since the pretransfusion testing functions are becoming more automated in hospitals and centralized in some communities, these laboratory functions will probably decrease in importance in the coming years. As a parallel development, transfusion services and their leadership will need to emphasize their critical role as transfusion consultants for clinicians, who will be
faced with a growing menu of product modifications and new offerings from donor blood or the recombinant engineers. If laboratory functions are reduced by testing automation, product manipulations such as antigen stripping and reduced alloimmunization from product manipulations or treatment options, the traditional hospital blood bank could have its role diminished. On the other hand, if we embrace the growing heterogeneity of products we can offer from donor blood, recombinant proteins, cellular engineering and bone and tissue banking, and continue to offer these services with emphasis upon our critical consultative role, the transfusion medicine discipline will continue to grow and flourish with benefits to patients and their supporting clinicians.

Alternatives to transfusion

The progress in another area of growing activity is documented in the chapter on patient blood management. Although the risks of infectious complications have been dramatically reduced in recent times, given their choice, many patients continue to search for transfusion options that would drive these risks even lower. The continuing perception of unnecessary transfusion risks led some hospitals to develop programmes to provide medical care to patients who refuse to receive transfusion support for religious reasons; in many cases, other concerned patients reluctant to receive blood were made aware that they might avoid transfusion support by taking advantage of the practices developed to address the needs of religious objectors. These programmes have emphasized the development of impeccable surgical techniques, the recruitment of physicians willing to care for these patients understanding this therapeutic limitation, the use of transfusion alternatives, the restriction of transfusions to lower triggers based upon evolving clinical evidence and the need for presurgical assessments and informed consent discussions with patients well in advance of surgical procedures.

Although the evidence base for these practices remains somewhat anecdotal and is derived at best from heterogeneous cohorts, the practices that have been developed for bloodless medicine have formed the basis for patient blood management programmes where the lack of supporting evidence for many transfusion interventions is driving the performance of clinical trials to provide evidence going forward. Patient blood management offers transfusion medicine a growing opportunity to provide better care through evidenced guided transfusion support, develop new products to reduce the risk of documented adverse transfusion effects and reduce the costs of unnecessary and potentially harmful transfusions for patients and hospitals.

Our enthusiasm for transfusion alternatives has been somewhat squashed by recent developments in the field. The advantages of pharmacological alternatives to blood (sterility, dose standardization, lack of immunogenicity) led to enthusiastic use of erythropoietin to stimulate red cell production, aprotinin to reduce intraoperative blood loss and VIIa to promote rapid haemostasis. Ensuing reports of adverse effects with these agents has led to more cautious use of these products for more limited indications and removal of aprotinin from the market. The long search for a haemoglobin-based oxygen carrier (HBOC) to replace blood in trauma was impeded by clinical trial evidence from a major trial in trauma showing limited efficacy and a meta-analysis demonstrating that the HBOC class has adverse effects of increased myocardial infarctions and mortality compared to controls as a result of nitric oxide effects. While a continuing clinical need for patients with severe anaemia who cannot be transfused due to auto-antibodies, alloantibodies or religious objection remains unmet, recent developments lead to the pessimistic conclusion that blood substitutes will not be available in the foreseeable future.

Cellular and tissue therapy and organ transplantation

The hospital transfusion service has expanded its limited, traditional portfolio (blood components and associated services) to provide support for developing cellular therapy needs in many hospitals. Moving beyond routine transfusion support and expanded HLA and blood grouping activities to support complicated transplant recipients, many transfusion services now provide graft engineering support, collection support for peripheral blood haemopoietic stem cells and tissue and bone banking services. In many cases,
these activities originated in haematology–oncology laboratories; as these activities have expanded their scope and providers have addressed the needs to augment their regulatory compliance, providing services to patients outside of the oncology realm, the hospital transfusion service has taken on these clinical laboratory responsibilities on its own or in conjunction with oncology-based laboratories. As cellular therapy services become more broadly required in disciplines such as cardiology, neurology and orthopaedics, this transition from separate discipline managed services to a centralized facility managed by transfusion medicine professionals has become an increasingly wise approach. In areas of the country or the world where hospitals may lack these capabilities, these functions can also be assumed and managed by a blood centre or national transfusion programme.

As transfusion medicine continues the transition to include cellular therapy, it is encouraging to note the increased attention and involvement by our discipline in therapeutic apheresis. Extending our services to offer direct patient care throughout the hospital provides an important clinical outreach activity for transfusion physicians, enabling us to be better recognized as clinicians by our colleagues and making our consultative activities in traditional transfusion support more likely to be sought and tolerated. It moves us beyond the role of the telephone police, rejecting unnecessary requests for transfusion support, to a role where we can readily demonstrate our primary concern for patients and not hospital expenses. Involvement in therapeutic apheresis also provides an important bridge to our provision of cellular therapy support to other clinical disciplines.

**Development of the evidence base for transfusion**

One of the most encouraging developments of the recent past is the recognition of our lack of robust evidence to support transfusion therapy decisions and some initial success in designing and implementing studies to fill this mounting void. These gaps have become more apparent as transfusion authorities and clinical transfusion prescribers have attempted to develop transfusion guidelines to improve transfusion practice and remove the burden of unnecessary transfusions, which are wasteful of resources and potentially harmful to blood recipients. As these groups have strived for consensus, it has become apparent that the strength of these guidelines is constrained by the level of evidence that supports the recommendations. We can thank a growing number of epidemiologists and transfusion authorities who have become converts to the epidemiology cause for moving us on the path to correct these deficiencies.

A major challenge for transfusion medicine is reconciling the differing levels of evidence we must consider for provision of blood components and recommending clinical transfusion practices. In the blood safety arena, it has been deemed inappropriate for us to wait for substantial evidence to change our practices if we believe that patients may be at risk, a concept deemed as the precautionary principle. In many cases, we have implemented changes in donor screening and testing based upon unproven assumptions that were clearly not cost effective or based upon statistically significant data collections. These actions are now taken more commonly because of the medicolegal and political risks of waiting for definitive proof of efficacy before taking action on blood safety issues.

Our decision making can be more rational in clinical practice where we can look at the available evidence for practice and design controlled clinical intervention trials to determine the best course for subsequent actions. In some cases the results of well-designed trials have been counterintuitive, such as the Transfusion Requirements in Critical Care (TRICC), which showed that less may be more when applied to transfusions in the ICU. In other cases, carefully performed studies implemented by transfusion practitioners have become available to prove that lower platelet transfusion triggers are acceptable for patients with haematologic malignancies. Based upon these trials, practice guidelines carry more weight. We need to be careful, however, not to overextend the interpretation of clinical trial data beyond the scope of the study populations; as an example, we understand that low platelet counts are acceptable in oncology but we have not performed clinically robust studies to determine the appropriate platelet thresholds in trauma or whether platelets stored at room temperature to maximize in vivo survival provide sufficiently rapid haemostatic correction in trauma situations.
The editors of *Practical Transfusion Medicine* clearly anticipated the importance of this area in earlier editions of the book and their prescient wisdom has rewarded readers with discussions of the mechanisms of trial design, how to evaluate evidence from trials and other data collections, and how to apply these findings to clinical practice. The fourth edition continues on this path, with evidence-enriched early chapters on specific practice issues and modified discussions of taking the next logical steps.

**Afterthoughts**

I appreciate the editors’ invitation to provide this rambling retrospective view of the evolution of transfusion medicine. I came into the field at a time when transfusion practices were rarely questioned, cost pressures were minimal and the overriding concern was the development of a sufficient donor base to meet the growing demands for red cells and platelets. HIV and viral hepatitis brought this quiet era to an abrupt end, generating a revolution to embrace blood safety as a pre-eminent cause and generating incisive questions from patients and the physicians about whether they really need the blood we could provide and what they might do to avoid the risks. Our track record to enhance blood safety has been remarkable, but new infections, haemovigilance systems that demonstrate persistent noninfectious problems for patients and conflicting clinical data that suggest that blood transfusions are a two-edged sword continue to perplex us. We are addressing these concerns with clinical trials, innovations in blood component design and expansion of transfusion services beyond our traditional boundaries. *Practical Transfusion Medicine* reviews much of the recent history, provides an update of where we are in this expanding field and reminds us of the continuing challenges that we must address. The ‘interesting times’ are clearly not over.

**Further reading**


PART ONE

Basic Principles of Immunohaematology
Cellular basis of the immune response

Leucocytes from the myeloid and lymphoid lineage are the key effector cells of both the innate and adaptive immune system, and are differentiated from haemopoietic stem cells (HSC) in the bone marrow.

Innate immune cells

Phagocytes and antigen presenting cells (APCs)
Cells of the myeloid lineage include monocyte-derived macrophages, neutrophils (polymorphonuclear neutrophils, PMNs) and dendritic cells (DCs). All three function as phagocytes that remove dead cells and cell debris or immune complexes. Foremost, these cells act as the first line of innate defence, ingesting and clearing pathogens. Very important in this is their activation via specific receptors, termed PRR (pattern recognition receptors) by danger signals derived from pathogens or inflamed tissue. This triggers their differentiation and their expression and/or secretion of signalling proteins, which lead to further activation of the immune response. Some of these proteins (like IL-1, IL-6 and TNF) increase acute phase proteins that activate complement, while others (chemokines) attract circulating immune cells to the site of infection. DCs, and also macrophages, additionally serve as APCs that process and present digested proteins as antigen to specific T cells of the lymphoid lineage. PRR ligation in this setting induces maturation of APCs with acquisition of chemokine receptors, which allow their migration to the lymph nodes where the resting T cells reside. Simultaneously, mature APCs acquire costimulatory 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 formation of defined cytokines and with it an optimal pathogen class-specific immune answer, with minimal tissue damage.

NK lymphocytes
Natural killer (NK) cells are capable of killing virus-infected cells either specifically targeted by the presence of antibody on the cell’s surface (antibody-dependent cell-mediated cytotoxicity – ADCC) or through the recognition of changes in the infected cell surfaces. Moreover, NK cells are normally kept from killing by expression of inhibiting receptors that recognize the presence of self-MHC molecules (see below) on autologous cells. Allogeneic cells with non-compatible MHC but also aberrant autologous cells (e.g. tumour cells) with lowered MHC expression lack sufficient of these NK inhibiting structures and trigger the default killing potential of NK cells.

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). For the large majority of T cells this is an alpha and a beta chain, which form a structure that is similar to the specific antigen binding site of immunoglobulin molecules. Immature T cells initially express a TCR receptor in complex with CD4 and CD8 molecules, which respectively interact with major histocompatibility complex 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-cell maturation into 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 the MHC complexes that express the self-antigen. 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 costimulatory molecules CD80 and CD86 on the APC with CD28 on the T cell subsequently drives the activated T cells into proliferation. Without this costimulation (e.g. by not fully differentiated APCs by insufficient or absent PRR ligation), T cells can become nonfunctional (anergized). The requirement of PRR-induced danger signals thus forms a second checkpoint of T-cell activation to prevent reactivity to self-antigens. Additionally, APC-released cytokines direct T-cell differentiation.

While immunoglobulins bind to amino acids in the context of the tertiary structure of the antigen, the TCR recognizes amino acids on small digested antigen fragments in the context of an MHC molecule. As indicated, there are two classes of MHC (called human leucocyte antigens of HLA in humans) molecules that are similar in their two polypeptide structure with an antigen binding groove (see Chapter 4). The MHC is polygenic determined, resulting in different sets of peptide binding specificities. Moreover, MHC genes are polymorphic, with many allelic variations in the population. Both MHC characteristics ensure 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. To be loaded on to MHC I, proteins need to be processed in smaller antigen parts by the proteasome. Subsequently, processed proteins are shuttled into the endoplasmatic reticulum for loading on to newly synthesized MHC class I molecules. Finally, this complex is cell surface expressed. CD8+ cytotoxic T cells (CTLs) recognize the MHC class I/antigen complex on the cells. Although viruses and parasites (like Plasmodium falciparum) can hide in red blood cells because the latter lack MHC, 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. Upon cell activation these proteins are protease digested in acidified endocytic vesicles yielding smaller antigen fragments. Again after fusion with the MHC class II containing compartments, the antigen is loaded on to the MHC class II molecule and routed to the plasma membrane. The described antigen expression routes, however, are not absolute. Specialized DC in this respect can also express viral and other extracellular-derived proteins on MHC class I to CD8+ CTLs while, vice versa, primarily cytosolic proteins via so-called autophagy can become localized in the endoplasmatic system and become expressed in MHC class II. This so-called antigen cross-presentation adds flexibility to the adaptive immune response.

Paradoxically, having described the fact that T cells become activated only when the specific TCR recognizes antigen in the context of its own MHC (termed MHC restriction) seems to refute the condition that MHC/HLA mismatched tissue transplants are rejected. Many acceptor T cells, however, can be activated because their TCR perceives donor-specific MHC as foreign in itself. 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 immunization.

**T helper (Th) cells**

Differentiation into T helper cells is dependent on signals (cytokines and/or plasma membrane molecules) derived from the APC. Different Th subsets can be characterized by their cytokine release and their extra-lymphatic action in infected tissues. Th1 cells release