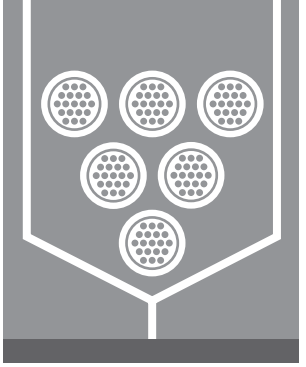

Perioperative Transfusion Medicine

SECOND EDITION

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Lippincott Williams & Wilkins
a Wolters Kluwer business
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Acquisitions Editor: Brian Brown
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Design Coordinator: Teresa Mallon
Production Services: Schawk, Inc.
Printer: Edwards Brothers

530 Walnut Street
Philadelphia, PA 19106 USA
351 West Camden Street
Baltimore, Maryland 21201-2436 USA
LWW.com

Printed in the USA

Library of Congress Cataloging-in-Publication Data
Perioperative transfusion medicine / edited by Bruce D. Spiess, Richard K. Spence, Aryeh Shander. — 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-7817-3755-9 (alk. paper)
1. Hemostasis, Surgical. 2. Blood—Transfusion. I. Spiess, Bruce D. II. Spence, Richard K. III. Shander, Aryeh.
[DNLM: 1. Blood Transfusion. 2. Intraoperative Care. 3. Postoperative Care. 4. Preoperative Care. WB 356 P4449 2006]
RD33.3.P47 2006
615'.39—dc22

2005030260

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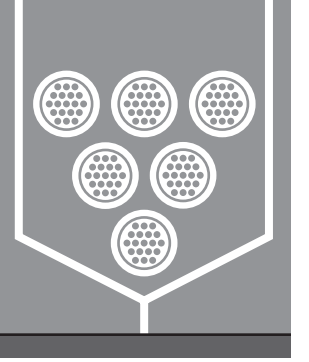
10 9 8 7 6 5 4 3 2 1

I dedicate my academic creativity encompassed in this book to Heather Austin Spiess, my wife, confidant and supporter. Her love, honesty, organization, and overwhelming calmness have buoyed my focus to develop this text in so many immeasurable ways.
BDS

To my wife, Claire, who helps make all I do possible, and to my family, who makes all I do worthwhile.
RKS

To my parents for their years of encouragement.
To my children for giving me a wonderful future.
To my wife, Susan, whose love and dedication make it all possible.
AS



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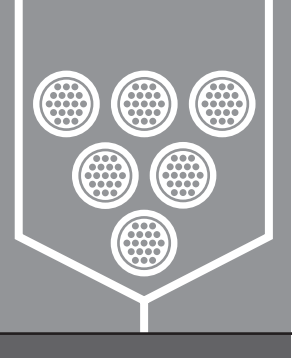


Preface

In 1998 *Perioperative Transfusion Medicine* was published. Within four years demand for a second edition was present throughout the surgical and anesthesia sub-specialties. When approaching a second edition, it was obvious that radical change had occurred within transfusion medicine since the mid 1990s. Normally, a second edition would present revisions of each chapter, building upon the foundation of the prior edition. After examining the first edition, it was clear that the second edition must reflect that the entire concept of transfusion for patients in surgery had undergone a revolution. Many of the authors that had contributed to the first book were not part of the latest aggressive changes in transfusions for surgery. Therefore, the book presented to you now, ostensibly a second edition, titled *Perioperative Transfusion Medicine,* is largely new and wholly different.

Transfusion medicine has evolved greatly since its inception. Risk has always been a part of blood transfusion from the first human experiments in the 17th century to the 21st century. Testing based on the ABO-rH immune cellular recognition system discovered at the turn of the 20th century has made major incompatibility errors a problem of human error alone. The introduction of citrate anticoagulation/preservation fostered the development of blood banks and eliminated the risks of direct transfusion. In the 1940s as the Second World War raged, the harvest and separation of plasma for military use answered a logistical need and led to the ability to produce packed red cell units, plasma, cryoprecipitate and specialized fractions such as gamma globulin and anti-hemophiliac factors.

The growth of transfusion as a mainstay of "modern" medicine accelerated with demand for blood, always pushing the blood banking specialists and industry to harvest more. During the Vietnam War banked blood was shipped from the western United States to the theatre of operation to support troops in the battlefields. Of interest, "Da Nang Lung" or what we now know as acute respiratory distress syndrome (ARDS) was first described in that war. Today, the United States Food and Drug Administration (FDA) lists transfusion related acute lung injury (TRALI) as one of the top three contemporary risks of transfusion. Was the ARDS of Vietnam the TRALI of today?

From 1971 until 1987 the utilization of red cell transfusions more than doubled in the United Sates. The use of platelets grew over 50 fold. In the 1970s the national hepatitis study reported on 300,000 patients with hepatitis who had been followed to find out how many patients required re-hospitalization per year and how many died (approximately 1,000 per year). In that time period no one asked the most basic question: did we as physicians know when a transfusion was beneficial or detrimental? Today we still do not know the answer to that question.

It was not until the outbreak of the human immunodeficiency virus (HIV or AIDS) epidemic that the lay public pressured the medical community into taking a close look at its transfusion practices. Blood bankers in Europe paid the price of incarceration for some of their handling of anti-hemophilic factor and the spread of the HIV epidemic to the unfortunate population of hemophiliacs. The blood-banking world has responded to the lay and government pressure by creating a voluntary blood donation system with ever expanding self-exclusion criteria. More importantly, the establishment of surrogate tests and ultimately nucleic acid testing (NAT) for key DNA fragments of hepatitis and HIV genomes have established the "safest blood" ever in our blood banks.

For that advance, the "safest blood" ever, the public and the surgical world should breathe a collective sigh of relief. However, reducing the risk of HIV and hepatitis transmission by transfusion is not good enough. The most basic question of all still remains: does transfusion of banked blood improve outcome for patients?

Only in the last 5 years has that most basic question begun to be addressed. The new data on outcomes requires a new focus.

Prior to the mid 1990s the focus of perioperative transfusion had been upon when was it most appropriate to transfuse and at what "trigger" should or could one transfuse. The pervading thinking at that time was that patients should be transfused when they hit a trigger of 10gm/dl hemoglobin/30% hematocrit or if they had lost 15% or more of their circulating volume. In 1987 the National Institutes of Health (NIH) consensus conference on red

cell transfusions concluded that the old "10/30" rule should be abandoned in favor of a decision to transfuse based on the patient's demonstrated clinical need for improved oxygen delivery. Since that time research has been focused on defining these characteristics. As a result, the transfusion trigger has been steadily creeping lower with more vague caveats for when it is appropriate to transfuse.

Almost every major surgical and anesthesia society has adopted guidelines for transfusion that largely echo the NIH consensus conference. As this preface is being written the American Society of Anesthesiologists is re-writing their guidelines for transfusion. In the absence of evidence-based transfusion indications, prevailing thought leaders still focus upon a given hemoglobin or hematocrit as the "trigger" point for transfusion. Unfortunately, many practitioners continue to transfuse based on this alone. This reliance on an arbitrary transfusion trigger signals that we, as clinicians, still do not have either a clear understanding of the clinical signs and symptoms of early oxygen deprivation or a reliable measure of whole body or tissue oxygen deficit. With such methods we could individualize the need for blood transfusion rationally based on the ultimate physiological goal, that is, to improve tissue oxygen delivery.

The most basic tenet of all medicine is to do no harm (Hippocrates: "As to diseases, make a habit of two things—to help, or at least do no harm"). We must address this in transfusion medicine in response to the rapidly growing evidence that transfusion of allogeneic blood has an association with worse patient outcomes. Ultimately, the decision to transfuse must be based on an evidence-based assessment of benefit versus risk.

The second edition addresses the findings that transfused patients often do worse in terms of length of hospital stay, serious postoperative infection, length of stay in the intensive care unit, renal failure and even long term mortality compared to those not transfused. Contributors also provide analyses of how these outcomes may be diminished or avoided. The second edition also differs from the first in spending a considerable amount of time discussing our increased understanding of tissue oxygen delivery and consumption, the role of the microcirculation in the transfer of oxygen, and the cellular mechanisms of shock. Contributing authors discuss how that knowledge might be utilized to guide one's thinking about when to transfuse.

The book is divided into eleven sections. The introductory section starts with a look at the history of transfusion to set the stage for today's practices. Chapters on the economics of blood and transfusion that follow acknowledge that the provision of blood and transfusion services today is one of the most rapidly inflating cost centers for hospitals. Contributing experts in their fields address the economic impact of our current struggle to provide blood that is both sufficient to meet our demands and safe enough for use. The introductory section concludes with a chapter on ethics. The ethical issues surrounding the transfusion of blood are complex and cannot be completely covered in a single chapter, so we have added a chapter (Chapter 37) that deals with the ethical challenge of the patient who refuses transfusion.

The second section delves deeply into the physiology of oxygen delivery. It begins with chapters presenting what is known about the microcirculation, followed by a more holistic look at how the cardiovascular and individual organ systems respond to anemia. Basic iron metabolism, red cell generation, and some new concepts in oxygen transport make this section radically different from the basic physiology presented in the first edition. Included in the section of basic physiology is a contemporary view of coagulation. The old view of one or more cascades of proteins driving the process of coagulation has been engulfed by the modern biology of cellular control and cross talk between cell lines. Hemostasis is presented as a very dynamic and carefully controlled process driven by cell signaling and interactive communication between inflammatory mediators and the vascular endothelium, an idea that is radically different from the traditional coagulation cascade concept. This approach to basic coagulation physiology will serve the surgeon and anesthesiologist reader well. If we re-learn the basics of coagulation and take on the contemporary view in daily practice, the practitioner will realize how Neolithic our standard coagulation testing is in relation to the beautiful complexity of the hemostatic/inflammatory system.

Section three focuses on transfusion risks, which are broken down into infectious risks, immunomodulation, and transfusion reactions. This section needs to be read by all surgeons and anesthesiologists since the risks of transfusion have changed dramatically since the first edition. Transfusion-transmitted infectious disease remains a threat in spite of advances in testing. Malaria remains the most common transfusion-transmitted infection worldwide. A myriad of other agents, ranging from parasites to prions, are known contaminants of the blood supply. We can identify some; others we cannot. Since the incidence of these infections remains at best an estimate, we cannot be complacent that because hepatitis and HIV are vanishing that we have defeated disease transmission in transfusion. Moreover, although the risk of contracting a transfusion-transmitted disease continues, it is not the most prevalent risk of transfusion. While the lay public and the media still focus upon these two viral infectious diseases, transfusion medicine specialists are addressing three far more common and serious risks today: immunosuppression, ABO-rH incompatibility (human error), and TRALI, all of which are as deadly as any disease. Experts in these areas provide detailed considerations of these problems.

Section four focuses on the basics of blood component therapy. Chapter 14 is titled to focus on the surgeon's perspective of blood banking. In reality the goal of this chapter is to help all non-blood bank professionals understand the processes that must occur within the blood bank in typing, cross matching, and cross checks to assure proper matching. A discussion of blood storage reviews existing processes and regulations that focus predominantly on the viability of the red cell. However, contributing authors chart important new territory in detailing both the biochemical deterioration and physical changes in erythrocytes caused by storage and their impact on oxygen delivery. The reader will be left with an understanding of the urgent need for further investigation and advances in this field.

A chapter on the role of quality control and the hospital blood utilization committee may seem to be a discussion of bureaucracy by the practitioner. In reality, the modern creative application of the blood utilization committee has driven and changed overall transfusion practice in a number of institutions. The use of a hospital blood utilization committee should therefore be looked upon as an instrument of constructive change. As the economics of blood transfusion change, hospital chief executive officers (CEOs) and key physicians should focus upon this chapter and review how their hospitals can manage their transfusion practices. Cost effectiveness of transfusion may need to be viewed not in terms of blood bank budgets and expenditures by the pharmacy for drugs, but in a whole hospital model of cost savings and improved patient outcomes.

Section five examines the emerging and changing world of alternatives to transfusion. Preoperative autologous donation (PAD) experienced a surge in utilization during the height of the HIV crisis followed by a backlash of negative sentiment over expense and waste in the early 1990s. Today its use has retreated from the earlier days, but as the cost of allogeneic blood increases and as shortages get greater, the discussion of which patients and what surgical procedures are appropriate for PAD is a very exciting and timely discussion. The use of erythropoietin increases and creates the most valuable oxygen carrier possible; the patient's own native and normal red cells. This one drug may well be underutilized today and it needs to be evaluated by any group or hospital embracing overall transfusion management. Oxygen therapeutics have been under development for over 25 years and have yet to bloom into a viable FDA approved therapeutic industry. These are often termed "blood substitutes" but they could provide so much more to modern medicine. In this second edition both the hemoglobin based oxygen carriers (HBOCs) and the perfluorocarbon emulsions (PFCs) are discussed with focus on what is new in the last seven to ten years. Clearly much more will be done with these fascinating technologies in the next few years.

Section six looks at trauma and the bleeding patient. This is the one place in medicine where most practitioners would find it easiest to agree upon the need for transfusion. Yet very few patients have massive blood requirements in trauma. A great deal is being learned about basic outcomes and transfusion through research reported in the trauma literature. For example, from the trauma literature we know today that there is a strong association between not only the total amount of blood transfused and multiple system organ failure, but that the age of the blood transfused is directly related to the severity of that organ dysfunction. Older blood is bad for more severely injured patients. Massive transfusion itself has risks including hyperkalemia, coagulopathy, and diffuse organ dysfunctions. Contributing authors take a careful look at the presumed benefit and the known risks of transfusion in trauma.

Section seven examines a number of coagulation issues. The primer for this section was put forth in the modern view of hemostasis previously discussed. Fresh frozen plasma is frequently overutilized today in many medical and surgical subspecialties. New data show these acellular products also carry risk, e.g., recent evidence shows that platelet transfusions are associated with a dramatic increase in stroke and mortality rate in coronary artery bypass surgery. Any decision making tree as to when to utilize these products has changed in the last five years. Therefore, the chapter on coagulation product usage offers recommendations on the appropriate use of not only FFPP, but also cryoprecipitate and platelet infusions. Platelet inhibitors are now one of the most widely prescribed groups of drugs in medicine. The use of these agents has profound effects upon whether patients will bleed in the operating room and post-operatively. The information regarding platelet inhibitors is largely new since the first edition. Agents and techniques to decrease bleeding are covered in the pharmacologic approaches and fibrin glue chapters. Once again, a number of changes and controversies have occurred with regards to the use of anti-fibrinolytic drugs (aprotinin and the lysine analogues). Questions regarding cost and efficacy of these drugs versus the relative costs and risks of transfusion are changing drastically. As a unit of red blood cells becomes radically more costly even those drugs that previously had appeared expensive are now appearing considerably cheaper.

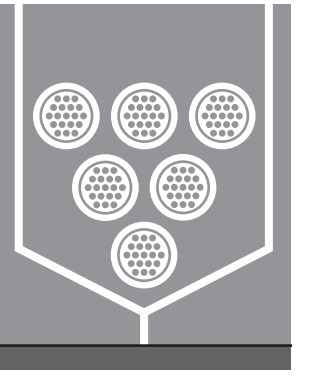
Section eight includes chapters on anesthesia and surgical practices that affect bleeding, coagulopathy and patient outcome. Any surgical procedure requires planning and forethought to utilize techniques such as regional anesthesia, euvolemic hemodilution and cell salvage. Although some of these techniques such as cell salvage may come under the purview of perfusionists or salvage technicians, it is ultimately a shared responsibility between the anesthesia and surgical team to think in advance and plan for those cases in which they could salvage the patient's own red blood cells.

Sections nine and ten focus attention on a number of surgical sub-specialties. In these sections, one size clearly does not fit all. The pediatric heart patient may have different criteria for transfusion as opposed to an elderly woman undergoing a radical hysterectomy or a routine abdominal operation. Therefore, although one may find a great deal of specific information for cardiac surgery or neurosurgery, be aware that concerns and practice for transfusion may not be applicable across specialties. More importantly, the sub-specialist should resist the temptation to simply open to the chapter pertaining to his/her cases and read only that area, since sub-specialty transfusion concerns are based on many of the preceding foundation chapters.

Section eleven serves as a concluding segment with Chapters 46–49 presenting the heart of the book. Outcome data from recent data-based research about the use of blood products and new scientific evidence about oxygen supply and delivery by blood transfusions found in earlier chapters feed into the discussion of the transfusion decision. These four chapters summarize this information while providing an up-to-date assessment of the thinking involved in the decision to transfuse. The reader should appreciate that this is a multifactorial and complicated process today with no easy answers, cookbook formulae, or guides. Chapter 48 looks at the risks of undertransfusing patients, and the book concludes with an emerging response to the contemporary complexity of transfusion.

The use of blood management has now become a central theme at many hospitals. Blood management does not mean simply decreasing blood utilization alone; it is a multidisciplinary and comprehensive effort with the goal of limiting transfusion to appropriate patients and situations. Unfortunately, the most "appropriate" transfusion is a moving target colored by differences of opinion among the experts (many of whom are contributors to this book) and by continued revelations in both clinical and basic transfusion science. Therefore, this book provides a summary of current understanding of transfusion science and practice rather than a simple, conclusive answer to when to transfuse.

In conclusion, as editors we understand this text takes a different, aggressive view of transfusion. It questions the very basic tenet of transfusion and cautions many in the surgical sub-specialties to look closely at their practice. The standard of transfusion practiced into the late 1990's is no longer acceptable in light of the major advances in the field. By the time this book is widely read more research will have been done that will change our standards for the better. Very little in medicine is changing as quickly as is transfusion.



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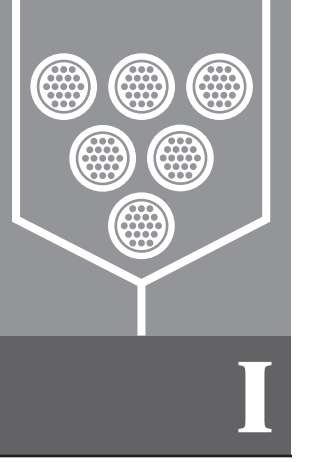

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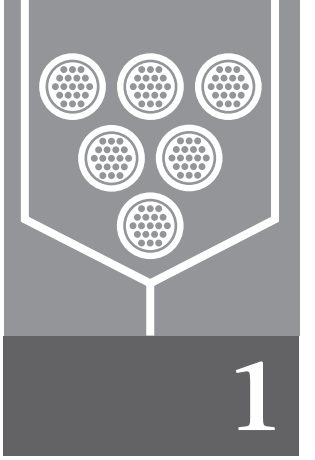
Introduction



A History of Transfusion

1

Bruce D. Spiess *Richard K. Spence*

DEVELOPMENT OF CLINICAL BLOOD TRANSFUSION

The first human transfusions were performed in France and England in 1667. Although there are apocryphal reports of blood being transfused to Pope Innocent VIII in the 15th century, the lack of means to transfuse blood makes this unlikely. As is true in much of medicine, 17th-century transfusions were the direct result of the development of technology coinciding with knowledge of anatomy and physiology, no matter how crude, that made an idea a reality. The sentinel events were the description of the venous circulation in *De Motu Cordis* by William Harvey in 1628 and Sir Christopher Wren's creation in 1658 of the first syringe made by fastening an animal bladder to a sharpened goose quill (Figs. 1.1 and 1.2). Wren was actually preceded in 1652 in the use of this device by Francis Potter, a British rector, whose choice of pullets as an experimental animal doomed his experiments to failure. Using larger animals, Wren was able to inject a variety of substances into veins. Building on these early experiments, Richard Lower performed the first animal-to-animal blood transfusions in a dog in 1665 in London, followed by a transfusion of lamb's blood given to Arthur Coga in London on November 23, 1667.

Although the first animal transfusion was performed in London, the French deserve credit for conceiving the idea of transfusing a human subject. A group of men, led by Jean Baptiste Denis, a professor of mathematics and philosophy in Montpelier, which included Paul Emmerez, a surgeon, Claude Tardy, physician to the Duc d'Orleans, and Robert de Gabets, a Benedictine monk, met in July 1658 in Paris to plan transfusion experiments (1). Having learned of Harvey's description of the circulation, de Gabets had conceived the idea of attempting blood transfusion. He solicited the help of a friar, Eloy Pichot, to make an instrument consisting of two silver cannulae connected to a small leather reservoir (Fig. 1.3). Each cannula had a valve that permitted only one-way flow. Experiments performed on dogs in March 1667 using this device were followed quickly by the first transfusion of animal blood into a human subject when Denis gave lamb's blood to a young man on June 15, 1667 (2). The patient was described as having an "intractable fever" and as being "possessed of an incredible stupidity" (2). Apparently, the boy did well enough after receiving nine ounces of lamb's blood to be considered a success. He was described posttransfusion as "possessing a clear and smiling countenance" (2). Although he developed shaking chills and "soot black" urine, this transfusion reaction was not enough to dissuade Denis from further transfusions (2).

This first transfusion was technically successful, but no clinical benefit as we would recognize it was achieved. The latter is not unexpected since the desired goal was to treat mental problems through the infusion of animal humors contained in blood. The religious significance of the blood of the lamb was quite clearly understood and intended. This medical fad continued for only a short period of time until a French patient, Antoine Mauroy, received two transfusions of calf's blood given by Denis in December 1667 (3). Mauroy, who had been an imbecile since childhood, had been found wandering the streets of Paris before being brought to Denis by his wife. Mauroy died following the transfusions; his widow brought suit against Denis and his colleagues and Denis countersued. In the investigation that ensued, the group was acquitted of the patient's death

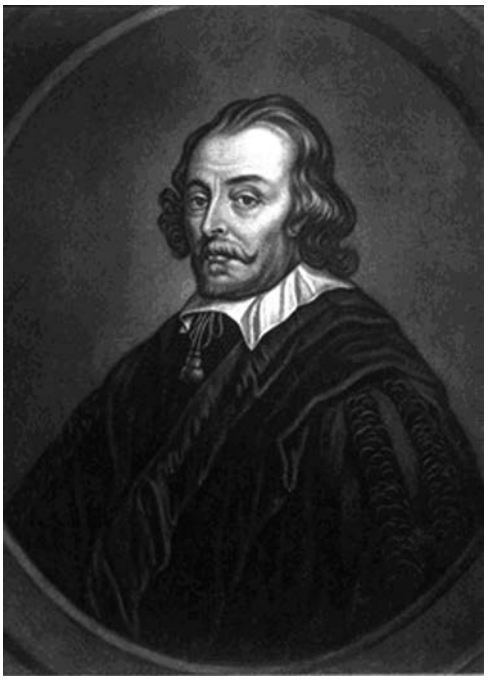


Figure 1.1 Sir William Harvey.

when the French courts determined that Mauroy's wife had poisoned him. However, the civil action was the deathblow to transfusion experimentation. The Edict of Chatelet, issued in 1668, quickly banned the procedure as dangerous and it disappeared from sight except for sporadic cases. Since transfusion had not been shown to have any measurable benefit, there was no movement to find a replacement.

Only sporadic reports of transfusion can be found during a period of 150 years, from the 1660s until the early

Figure 1.2 Sir Christopher Wren.

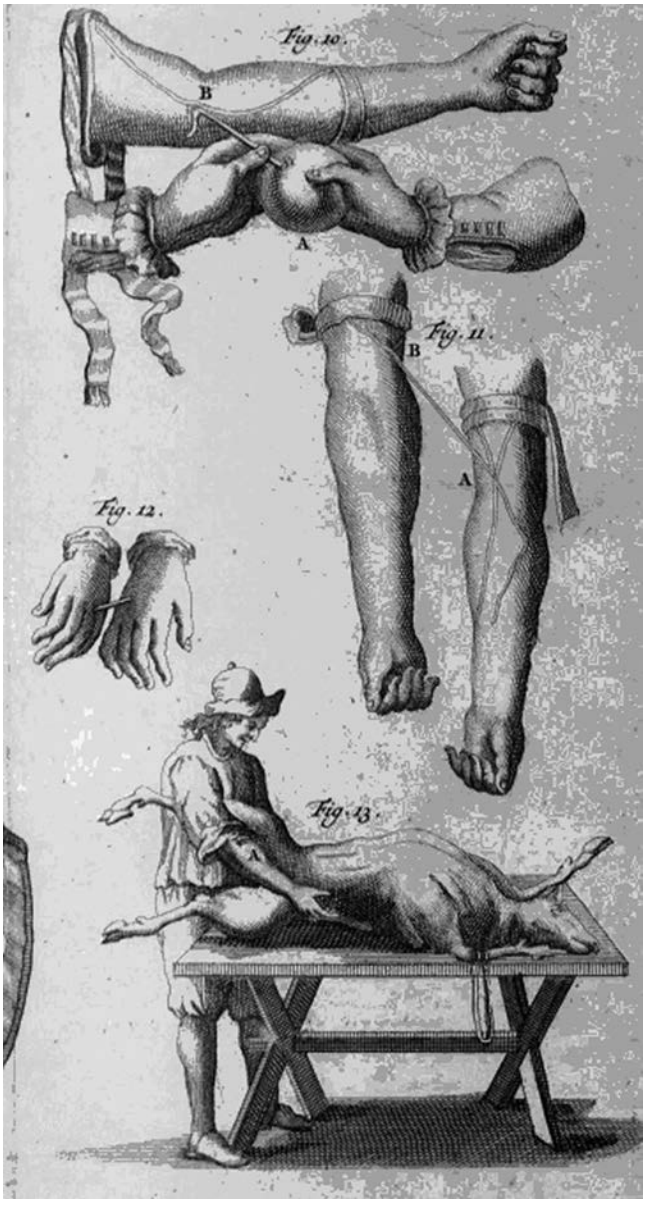


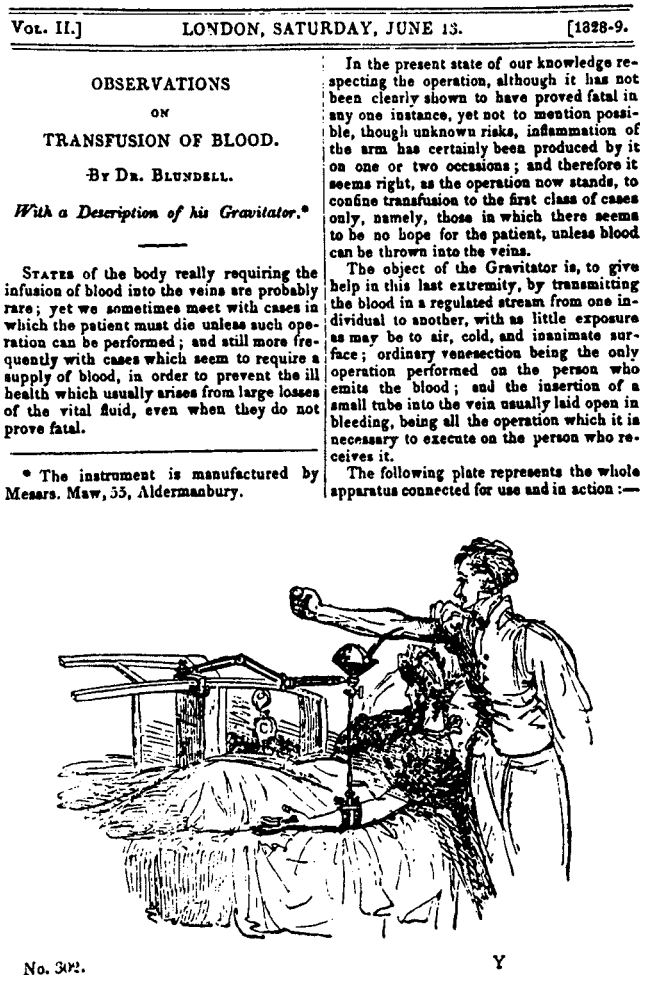
Figure 1.3 17th-century woodcut of transfusion.

1800s. During this time significant advances were made in both anatomy and physiology. The anatomy and functions of the heart and the circulation were defined. In 1774, Lavoisier clarified the role of oxygen in respiration and Priestley described the function of red blood cells as oxygen carriers. These discoveries set the stage for a new era of transfusion medicine. The credit for the rebirth of interest in transfusion belongs to James Blundell, (Fig. 1.4) a physician-surgeon practicing in London in the early 19th century. Alarmed by the unacceptably high number of deaths in his practice caused by postpartum hemorrhage, Blundell looked for a means to replace this shed blood. Blundell's interest prompted him to experiment first in the

Figure 1.4 James Blundell.

animal laboratory with interspecies transfusion, which led him to the conclusion that transfusing animal blood into humans was inherently unsafe (4). When faced with the daunting task of obtaining human blood for transfusion, he developed two approaches: (a) obtaining capillary blood from volunteer donors with a rather monstrous device, and (b) salvaging shed blood. He stirred or agitated the blood to defibrinate it, and then infused it through a gravitator or an impeller device. Four of his first eight attempts at human-to-human transfusion were successful (Figs. 1.5 and 1.6).

Blundell is considered to be the Father of Autotransfusion for his work in this field (5). He justly deserves credit as the first to use autologous blood for transfusion. However, we believe he warrants even greater recognition as the Father of Modern Surgical Transfusion Science for being the first to make the connection between the potential benefit of transfusion in preventing death from hemorrhage. This philosophy was a departure from the traditional view of blood transfusion based on Galenic principles of blood as a humor rather than as a physiological substance. Blundell's procedures are remarkable because he practiced medicine at a time when bloodletting to the extreme was widely accepted as appropriate therapy for most illnesses. Little regard was paid to the deaths caused by this iatrogenic hemorrhage. Battlefield approaches to bleeding were based on quick action and vessel ligation. Surgeons had made the connection between blood loss and death, but Blundell was the first to show that transfusion could be therapeutic (6). In



Vol. II.] LONDON, SATURDAY, JUNE 13. [1828-9.

OBSERVATIONS
ON
TRANSFUSION OF BLOOD.

By Dr. Blundell.

*With a Description of his Gravitator.**

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; and still more frequently with cases which seem to require a supply of blood, in order to prevent the ill health which usually arises from large losses of the vital fluid, even when they do not prove fatal.

* The instrument is manufactured by Messrs. Maw, 55, Aldermanbury.

In the present state of our knowledge respecting the operation, although it has not been clearly shown to have proved fatal in any one instance, yet not to mention possible, though unknown risks, inflammation of the arm has certainly been produced by it on one or two occasions; and therefore it seems right, as the operation now stands, to confine transfusion to the first class of cases only, namely, those in which there seems to be no hope for the patient, unless blood can be thrown into the veins.

The object of the Gravitator is, to give help in this last extremity, by transmitting the blood in a regulated stream from one individual to another, with as little exposure as may be to air, cold, and inanimate surface; ordinary venesection being the only operation performed on the person who emits the blood; and the insertion of a small tube into the vein usually laid open in bleeding, being all the operation which it is necessary to execute on the person who receives it.

The following plate represents the whole apparatus connected for use and in action:—

No. 302. Y

Figure 1.5 Blundell's gravitator. (Reprinted with permission from Blundell J. Observations on transfusions of blood. *Lancet*. 1828; 2:321.)

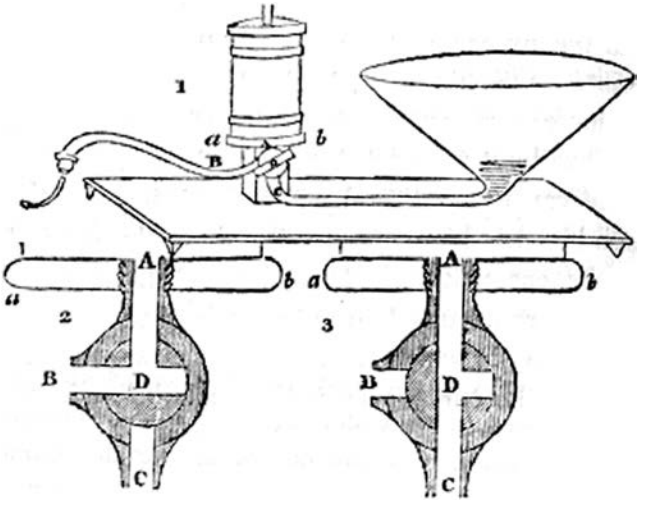


Figure 1.6 Blundell's impeller.

Figure 1.7 19th-century transfusion using variation of Blundell's gravitator.

addition, Blundell's rejection of animal blood as incompatible with human's predated Landsteiner's discovery of blood groups by almost 100 years.

Blundell's pioneering work reawakened the medical world to the therapeutic potential of transfused blood. Others modified and improved on his clinical experiments, to the extent that Jennings was able to compile and publish a bibliography and review of 243 transfusions performed before 1873 (Fig. 1.7) (1). During this period, our understanding of physiology and the effects of blood loss advanced rapidly. Claude Bernard established the concept of an internal milieu of checks and balances in the body and the need to maintain a steady intravascular volume to prevent death. In 1854, Le Dran defined metabolic derangement as the clinical entity of shock. The use of blood transfusion now had a firmer physiological foundation for use in clinical practice as a means of restoring blood volume.

However, multiple problems with blood hindered its regular use. Lethal transfusion reactions were a major risk of transfusion, thereby limiting the procedure to life threatening situations. Desired therapeutic benefit was by no means guaranteed. Although Jennings reported that 114 patients (46.9%) had had a complete recovery following transfusion, others did not fare so well. Blood was difficult to handle because of its rapid clotting time, which effectively eliminated even temporary storage and indirect transfusion. As a result, the field of clinical transfusion medicine was dominated by direct transfusion using donor artery to recipient vein surgical connections (Fig. 1.8).

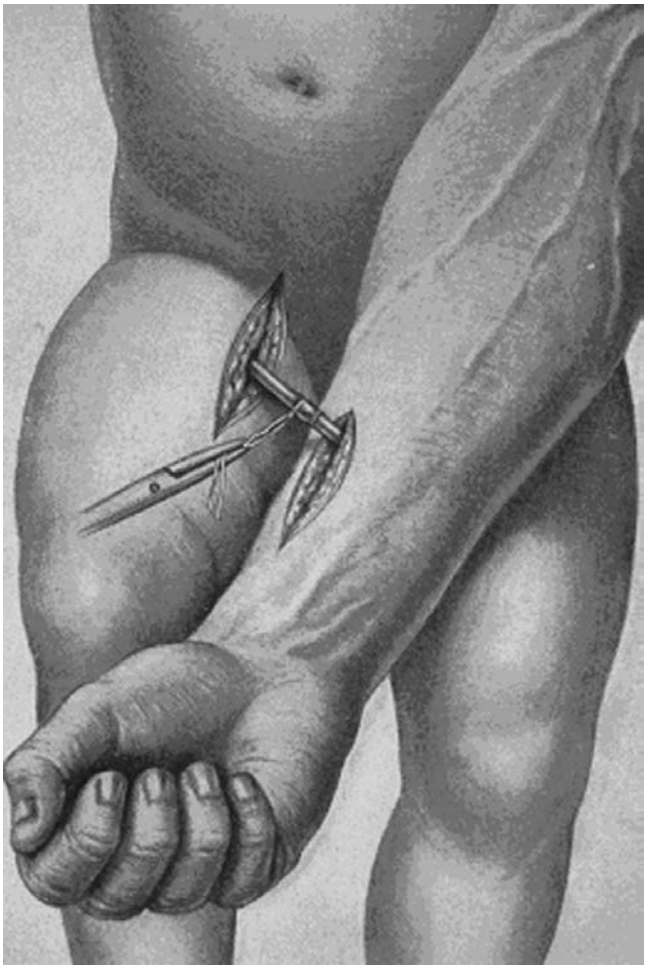


Figure 1.8 Direct transfusion—vessel to vessel.

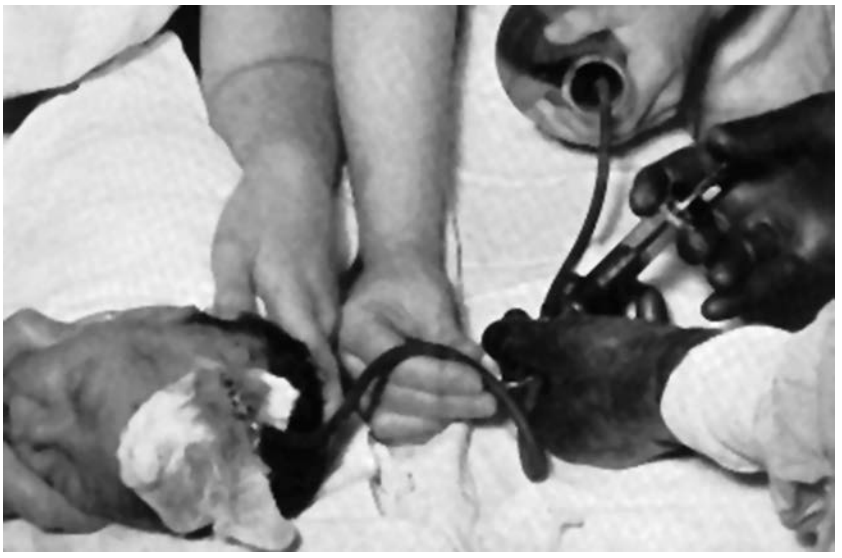


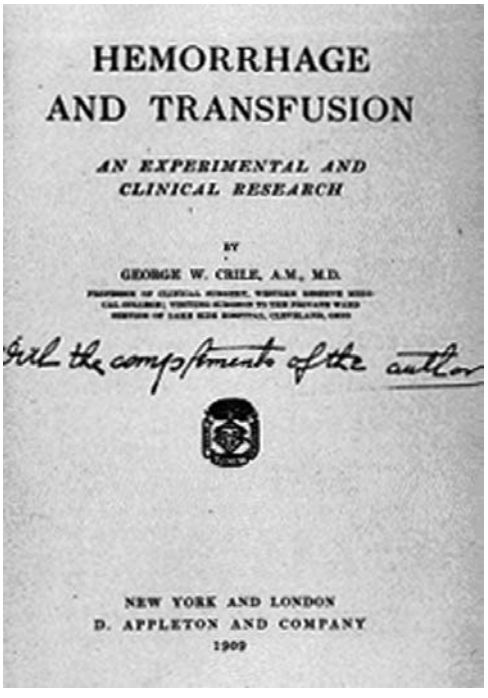
Figure 1.9 Indirect transfusion of citrated blood, ca. 1930.

Unfortunately, this approach, which required considerable skill, was cumbersome and permitted only one time transfusions. Early syringe and roller devices using two syringes or vein-to-vein tubing connections improved direct transfusion practices, but the problems of reactions, sterility, and volume overload remained (Fig. 1.9). These problems with transfusion prompted the search for an alternative as early as the mid-19th century.

As early as 1876, Barnes and Little described the use of saline solutions in the restoration of "equilibrium in the circulatory system" (3). Further experiments with this first blood substitute established a firm role for crystalloid infusions in the treatment of hemorrhage. Hamlin tried infusions of milk as a blood replacement, reasoning that the white corpuscles of blood came from the same source as milk (7). Fortunately, this approach was short-lived. Saline provided some advantages and was used in conjunction with the newly developed general anesthesia that permitted more involved surgery.

In the late 1800s, Rudolph Virchow postulated that malignancies traveled via the lymphatic system where they were trapped. This led to the inception of radical excision of cancers and their lymph node groups, e.g., radical mastectomy and abdominoperineal resection. Excessive hemorrhage as a hazard now moved from the battlefield into the elective surgical suite. Halsted's description of uncontrolled bleeding as the only defense of the unconscious patient against the incompetent surgeon epitomized the new era of surgical training aimed at controlling blood loss (8). Surgeons trained by Halsted at Johns Hopkins spread the bible of gentle tissue handling, anatomic surgical approaches, and meticulous hemostasis that remain with us today as a mainstay of bloodless medicine and surgery. Even with this advance, blood loss remained an obstacle to the further development of surgery.

As the 20th century approached, some investigators tackled the problem of transfusion reactions, some searched for ways to store blood, while others improved our knowledge of when to transfuse. Crile consolidated our understanding of anemia, hemorrhage, and transfusion as a means of restoring blood loss (Fig. 1.10) (9).


HEMORRHAGE
AND TRANSFUSION

AN EXPERIMENTAL AND CLINICAL RESEARCH

BY

GEORGE W. CRILE, A.M., M.D.

With the compliments of the author

NEW YORK AND LONDON
D. APPLETON AND COMPANY
1909

Figure 1.10 Title page—George Crile, MD, Hemorrhage and Transfusion, 1909.

Landsteiner's description of the ABO red cell antigen system led to crude forms of testing that dramatically reduced the risk of death from transfusion reactions (10). Weil added citrate salts to blood, proving that this would retard coagulation. Lewisohn was the first to devise a safe combination of citrate that permitted blood to be stored temporarily. Rous and Turner, working at the Rockefeller Institute in New York, added dextrose to the citrated blood, thereby allowing storage for up to 21 days (11). Sporadic reports of transfusion using citrated blood began to appear. In the 1924 predecessor to the *Year Book of Medicine*, Ocshner discussed the value of citrate in prevent coagulation with stored blood and commented on the relative value of citrated over fresh blood in treating hemorrhage (he favored whole blood). He further described the use of autotransfusion in a 51-year-old male who had bled from splenic trauma. He collected 800 cc of blood from the abdominal cavity, strained it, added citrate, and reinfused it successfully through an arm vein (12). In the same year book, Robert Preble, MD, Professor of Medicine at Northwestern, discussed a series of over 400 direct transfusions performed by Dr. W.W. Duke and Dr. D.D. Stofer in Missouri. These physicians pronounced transfusion as "harmless if the right donor is chosen, immediate in providing results and permanent," depending on the disease condition (13). Preble's editorial response confirmed widespread concerns about the use of transfusion for any condition other than trauma: "One cannot agree with any of the three conclusions. It (transfusion) may be harmful and the results are neither immediate nor certain."

Much of this landmark work was completed just in time for blood to be used at the front in World War I. However, it created a whole new set of problems of the need for a donor supply and how, where, and for how long to store blood. Russian physicians, led by Filatov, Depp, and Yudin pioneered the collection and storage of cadaver blood (14). This approach met with great disfavor in the West, but it formed the basis for the development of the first blood bank in Chicago by Seed and Fantus in 1934. Their unique contribution was twofold: development of a facility to store blood and the use of live human donors.

The onset of World War II created the need for modernization in transfusion delivery as well the need for a suitable substitute. British blood services responded with both direct and indirect battlefield transfusions. Work presented at the American Human Serum Association meeting in 1941 focused on the need for the United States and Canada to prepare a wartime supply of blood and blood products. This work is summarized in the monograph entitled *Blood Substitutes and Blood Transfusion* edited by Stuart Mudd and William Thalhimer (15). Thirteen million units of blood and blood products were contributed by United States citizens for use by the Armed Forces between 1941 and 1945. The realization that the United States now collects the same number of units in one year reflects how much the business of blood banking has grown.

Sixty-five authors contributed to the two-volume, 1941 *Surgery of Modern Warfare* text that consolidated British experiences (16). F. Ronald Edwards, a research assistant in the Department of Surgery at Liverpool University, described the process of preserving blood but devotes only two short paragraphs to the limitations of transfusion with stored blood. He states that stored blood is "ideal" for acute hemorrhage and shock, but that it is less effective in cases of sepsis (16, p. 43). He also recommends the concomitant administration of "massive iron therapy." No results from blood transfusion are reported (16, p. 43).

White and Weinstein (17) described lessons learned in World War II in their 1947 book on then-current transfusion practices. Topics included the use of human plasma in treating shock on the battlefield and plans for the adaptation of its use to civilian settings. A variety of gelatin-based and animal derivative substitutes that were under investigation were described as well as protein hydrolysates, the clinical precursors of hyperalimentation solutions. Substitutes saw little use during World War II. Mudd and Thalheimer's book contains state-of-the-art chapters on preparation of dried human plasma, early work on hemoglobin-saline solutions by Amberson, and the use of casein infusions by Whipple. None of these was ready for extensive clinical use. For example, Amberson's (18) hemoglobin solutions produced significant renal damage and were rapidly eliminated from the circulation.

It became clear that transfusion had come of age when the Mayo Clinic faculty devoted 25 pages in their issue of the *Medical Clinics of North America* in 1947 to blood transfusion (19). The general opinion based on this huge wartime experience was that blood and blood products were safe for widespread human use. No one wished to return to the bad old days of animal products for transfusion when human plasma and albumin were readily available, effective, and safe. Physicians returning home after the war demanded that blood transfusion be available, so transfusion medicine entered an era of rapid growth secure in the belief that the benefits of transfused blood far outweighed the risks.

THE RISE OF ALTERNATIVES TO ALLOGENEIC BLOOD

Several major forces played pivotal roles in the development of transfusion alternatives and bloodless medicine

and surgery, including our increasing knowledge of the risks of allogeneic blood, the desire of Jehovah's Witnesses to have advanced medical care without transfusion, explosions in medical technology, and steady progress in our understanding of oxygen transport physiology.

Transfusion reactions were well documented and understood by the 1950s when blood transfusion practice expanded. Seldon (20) reported on transfusion reactions and treatment at the Mayo Clinic in 1956. Trobaugh and de Cataldo (21) described the major and minor reactions, including the possibility of bacterial growth in stored blood in 1959. Although the number of lethal transfusion reactions diminished with the introduction of routine typing and cross-matching, reactions still occurred. The ability to identify the Rh complex and multiple, isolated red cell antigens reduced the incidence of hemolytic and antibody-based reactions. It had been known for some time that blood transfusion transmitted syphilis, malaria, smallpox, and what was known as passive anaphylaxis. Although blood was known to transmit disease, the only one thought to be a public health concern in the United States was syphilis. Mandatory testing for spirochetes using the Venereal Disease Research Laboratory, or VDRL, test could prevent transmission.

Water began to seep through the dam as early as 1943 with reports of jaundice following the administration of blood products (22,23). These isolated reports raised little concern among the greatest users of blood—surgeons—primarily because they rarely saw the consequences of transfusion-transmitted hepatitis. Patients who developed this disease after surgical transfusion were long gone from the surgeon's practice. Milles et al. (14) raised concerns about this problem in their monograph on autologous transfusion published in 1971. They reported not only on the relationship between transfusion and hepatitis, but also on their experience with the use of both predonated autologous blood and autotransfusion to avoid allogeneic transfusion. Using this combination of alternatives, they were able to avoid allogeneic blood transfusion in 53.8% of all patients who underwent thoracic surgery at the Chicago State Tuberculosis Sanatorium during the 1960s. They collected 534 units of blood from 458 patients who had preoperative hemoglobin levels of 11 gm per dL or higher. Of these units, 522, or 98%, were transfused during surgery or within 48 hours. They extended this work to both general surgical and urological patients, accruing data on approximately 1,000 patients treated with alternatives. These early investigators were able to provide 90% of the surgical blood needs through autologous sources.

This pioneering work by Milles et al. (14) in autologous predonation and autotransfusion was prompted by their concerns about transfusion-transmitted hepatitis and medicine's inability to prevent its spread. Unfortunately, their work fell on deaf ears in most operating rooms in the United States, in part because of the need for allogeneic blood to support advances in surgical technology and treatment. Konrad Messmer of Germany, who has provided us with the understanding of hemodilution and the physiologic basis for its current clinical use, has spent his life investigating another approach to using autologous blood through hemodilution.

The availability of blood led to the development of what we have chosen to call transfusion-based surgical technologies and operations. These include cardiac, vascular, oncologic, and joint replacement surgery among others. Gibbon's invention of the first heart–lung machine in 1953 provided the means to perform surgery on the heart and great vessels. Blood was used to prime the pump in early machines with routine typing and cross-matching of 25 units of blood for single-vessel cardiac bypass operations in the 1970s. This extensive use of blood prompted surgeons and anesthesiologists to find ways of salvaging any leftover cells (5). Although Cohn had conceived of the idea of a cell separation device as early as 1953, the first prototype was built by Taswell and Wilson at the Mayo Clinic in 1968 (24). At the same time, Dyer and Klebanoff developed a cell salvage device through Bentley Laboratories (25). Blood collected by this first Bentley machine was contaminated with impurities that often led to coagulopathy. It also produced lethal air embolism. Improvements in separation technology helped combat these problems. Latham at Haemonetics Corporation devised a differential centrifugation bowl coupled with a collection reservoir containing anticoagulant that created a practical means for recovery of shed blood in the operating room during a variety of surgical procedures. Improvements in these devices over the years have led to the current range of cell salvage devices that are used in both the operative and postoperative periods.

One group of patients, the Jehovah's Witnesses, were unable to take advantage of these transfusion-based surgical technologies and operations, because of their religious beliefs that forbade them from accepting blood transfusions. Their desire to obtain the best possible medical care without the use of blood was met with scorn and derision by many in the medical community. Most physicians misunderstood the Witnesses position and labeled them as zealots who refused all medical treatment for themselves and their children. Few surgeons who did understand were willing to take on the problems of major surgery without transfusion. One of these few, Denton Cooley, was the earliest of the modern pioneers in bloodless medicine and surgery. His demonstration that open heart surgery could be safely performed without blood was published in 1977.

This report encompassed a 20-year experience including 542 patients ranging in age from 1 day to 89 years (26). Cooley's success provided a stimulus for others to offer surgical treatment to Jehovah's Witnesses. The most notable among these was Ron Lapin, a California surgeon, who operated on several thousand Witness patients during his surgical career. Moreover, he was the first to recognize bloodless medicine and surgery as a specialty or discipline. Based on this belief, he created the first bloodless medicine and surgery center at the Bellflower Hospital in California in the late 1970s and early 1980s in response to the demand for his services. He also published the first journal in the field and made the first efforts at training and credentialing physicians. The Watchtower Bible and Tract Society, the parent organization of the Jehovah's Witness religion, recognized the importance of providing educational assistance to physicians who were willing to treat their members. Early informal efforts at education and communication were given structure in 1988 with the introduction of the Hospital Information Services branch of the Watchtower in Brooklyn, New York. This group of individuals has become one of the primary sources of information to the medical community regarding transfusion alternatives.

Technological developments also played a significant role during this time, particularly in the field of blood substitutes. Gerald Moss and Stephen Gould in Chicago, Tom Chang in Montreal and Gerson Greenberg in Providence were among those early investigators who worked diligently on the production of a safe, hemoglobin-derived substitute for blood. Moss and Gould's systematic approach to solving the toxicity problems of these products has led to the production of polymerized hemoglobin, Polyheme, which is in clinical trials today (27). Tom Chang's continued quest for a liposome-encapsulated hemoglobin substitute has produced two significant side benefits (28). He has provided us with much needed information on oxygen transport physiology as well as a venue for discussion of blood substitute through both his biannual conferences and the journal *Artificial Blood Substitutes.* Greenberg's work on reducing hemoglobin toxicity has helped produce a safer product while expanding our knowledge about nitric oxide interactions with the endothelial cell interface (29). Perfluorocarbon-based blood substitutes saw the light of day in the early 1980s in the form of Fluosol DA 20%, a product produced by Green Cross of Osaka, Japan. It was the genius of Ryochi Naito, the company's founder, that coupled Leland Clark's work with raw perflourocarbons with Robert Geyer's development of intravenous lipid emulsions to produce this first artificial blood substitute (30). Clinical trials of Fluosol product in the anemic Jehovah's Witness patient in the early 1980s led to a myriad of advances in bloodless medicine and surgery (31). Although Fluosol was not proven to be of significant benefit in treating surgical anemia, its use stimulated us to redefine the role of temporary oxygen carriers and to focus on their correct potential use as transfusion alternatives. Duane Roth, Peter Keipert, and Simon Faithfull of Alliance Pharmaceuticals have built on this early experience to produce Oxygent, the modern perfluorocarbon oxygen carrier now in clinical trials. The Fluosol trials had a greater impact on those involved in the 1980s clinical trials the authors included. This was the stimulus for many to question long-standing teachings about the transfusion trigger and to reassess our use of allogeneic blood. Experience with treating Jehovah's Witnesses prompted one of the authors (RKS) to develop one of the first bloodless medicine and surgery centers at Cooper Hospital in Camden, New Jersey. Others sprang up in Chicago, Cleveland, and in Europe as time progressed. To date there are close to 200 such centers throughout the world (32).

Without question, the realization in the early 1980s that the HIV virus was transmissible by blood transfusion opened the eyes of both physicians and the public to the inherent risks of allogeneic blood. This reawakening coincided with many of the technological and scientific advances that allowed us not only to analyze blood in a more sophisticated and complete way, but also to take measures to ensure increased safety. The reader is undoubtedly familiar with the worldwide efforts and successes in this area. Unfortunately, many of the advances that have made blood safer, i.e., donor testing for bloodborne pathogens, have resulted in loss of donors, fewer available blood products, and tremendous costs. These consequences have, in part, stimulated physicians and scientists throughout the world to search for alternatives to red blood cells. We have modified surgical procedures, investigated and improved autologous strategies, explored the role of drugs, blood substitutes and sealants in minimizing blood loss, and the need for transfusion. Alternatives such as predonation, which has become a standard in joint replacement surgery, are now actively debated in the medical literature as to cost-effectiveness and appropriate use. Consensus conferences on the transfusion trigger and correct transfusion policies have been held in a variety of countries and by all major societies. Organizations such as SABM, the Society for the Advancement of Blood Management, the driving force behind this textbook, and NATA, the Network for Advancement of Transfusion Alternatives, are now in place. Blood substitutes, or oxygen carriers, are finally on

the clinical horizon and will revolutionize the way we understand and treat oxygen transport.

Although evidence-based use of blood has come a long way, there is still much to be done. Although most physicians understand the risks of blood, we cannot say with any certainty that we understand when transfusion is appropriate. Furthermore, education is still needed in the correct use of alternatives. Our understanding of the benefit of allogeneic blood in a clinical setting is now under scrutiny and will help redefine when and whom we transfuse. It is our hope that this text will be a source of inspiration to others who search for these answers.

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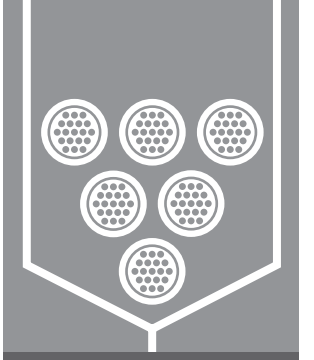


2

The Contemporary Economics of Transfusions

Timothy J. Hannon *Kathy Paulson Gjerde*

Blood products are a vital and integral part of modern health care and have been since the advent of the first blood bank in 1936. The foundation of the current blood banking industry was laid during WWII, when efficient methods of blood processing, handling, and storage were developed to meet the huge wartime demand. Tremendous advances in blood processing technology and blood screening in the latter half of the 20th century have resulted in steady increases in blood safety and availability. The National Blood Data Resource Center estimates that each year 14 million units of whole blood are collected and processed into 27 million blood products, which are then transfused to 4.5 million medical and surgical patients (1). The development of a safe and readily available blood supply has facilitated the advent of lifesaving procedures, such as trauma resuscitation, cardiac surgery, organ transplantation, and chemotherapy. None of these procedures could have come about, nor could they currently exist, without an efficient collection, distribution, and delivery system for these millions of units of blood products.

In essence, blood has become the oil of the medical industry, lubricating the gears of health care delivery. It is interesting to note that the blood market is currently facing a set of challenges similar to those found in its industrial market counterpart. In the crude oil market, rising world demand and an inability to quickly expand capacity have led to rising crude oil prices (2,3), as illustrated in Figure 2.1. The U.S. is also faced with an analogous crisis in the blood market, as blood demand threatens to outstrip supply and blood costs escalate. Local and regional blood shortages have become more frequent, leading to delayed hospital admissions and surgery cancellations. Blood fees more than doubled during the period 1998 to 2003 (4), creating a hardship for hospitals already dealing with thin operating margins and declining reimbursement.

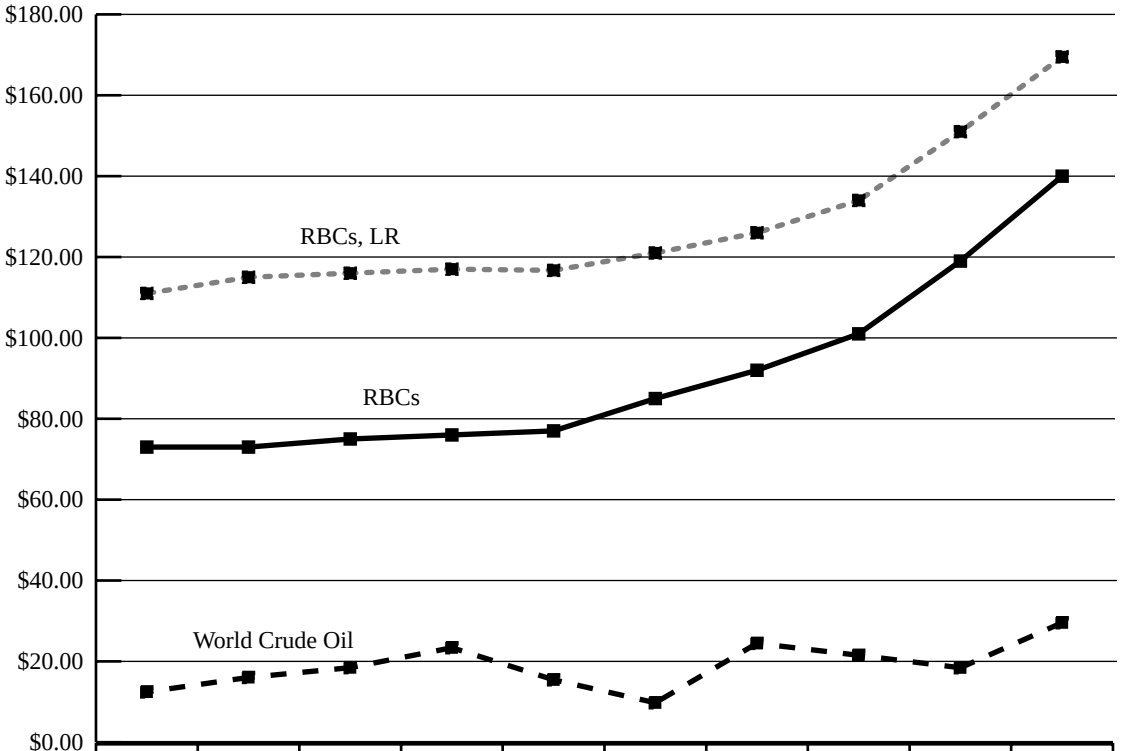
Although prices are rising in both the world crude oil and U.S. blood markets, this price increase seems to be more pronounced in the blood market in recent years (Fig. 2.1). In the next section, the reasons behind this discrepancy are examined using a demand-and-supply market framework. After providing a more in-depth explanation of what is happening in the current blood market, the impact of these events on health care organizations in terms of transfusion costs is assessed. Finally, alternative courses of actions that hospitals may pursue in response to blood market pressures are considered.

THE ECONOMICS OF THE MARKET FOR BLOOD

To better understand the availability and cost issues surrounding blood in the U.S., it is helpful to use the standard economic framework of a market. Like all markets, the market for blood consists of two parts, buyers and sellers.

Demand and Supply

On the demand side of the market, hospitals and other health care facilities purchase blood products for use in a variety of procedures. The quantity of blood products demanded in the overall market depends on a number of factors, including the age of the U.S. population, the types of procedures performed, and the per unit price of blood



	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
World Crude Oil	$12.45	$16.03	$18.45	$23.38	$15.45	$9.77	$24.46	$21.51	$18.43	$29.56
RBCs	$73.00	$73.00	$75.00	$76.00	$77.00	$85.00	$92.00	$101.00	$119.00	$140.00
RBCs, LR	$111.00	$115.00	$116.00	$117.00	$116.70	$121.00	$126.00	$134.00	$151.00	$169.50

Figure 2.1 World crude oil prices ($/barrel) and average red blood cell fees ($/unit) for America's Blood Centers, 1994–2003. Conditions in the world crude oil market have mirrored those in the U.S. blood market, producing similar results in terms of increasing prices. Adapted from Energy Information Administration. U.S. Department of Energy Web site. Available at: http://www.eia.doe.gov/pub/international/iealf/table71.xls. Accessed August 10, 2004; Starkey J. America's Blood Centers (written/oral communication). March 24, 2004.

products. Focusing on the relationship between the per unit price of blood products and the quantity of blood products demanded, it is possible to generate what is known as a demand curve for blood products. This curve shows how quantity of blood products demanded changes as the per unit price changes, holding all other factors (e.g., age, types of procedures) constant. In general, demand curves are typically downward sloping, indicating an inverse relationship between price and quantity demanded, as illustrated in Figure 2.2. In other words, as the per unit price of blood products increases (decreases), all else equal, the volume of blood products health care facilities are willing and able to purchase decreases (increases).

On the supply side of the market, community blood centers affiliated with the American Red Cross (ARC) or America's Blood Centers (ABC) are the primary providers of blood products to health care facilities. The quantity of blood products supplied in the overall market depends on several factors, including the cost of collecting and screening blood products, the number of active blood donors, and the per unit price of blood products. Again, focusing on the relationship between the per unit price of blood products and the quantity of blood supplied, it is possible to generate a supply curve for blood products. This curve shows how quantity of blood products supplied changes as the per unit price changes, holding all other factors (e.g., collection and screening costs, number of donors) constant. In contrast to demand curves, supply curves are typically upward sloping, as illustrated in Figure 2.2. In other words, as the market selling price for blood products increases, all else constant, community blood centers are able and willing to supply more blood products to the market given the increased profit potential of the market. Conversely, when the price of blood products is low, the reduced profitability of market makes it more difficult for these centers to supply blood products to the market, thereby reducing quantity supplied.

Market Equilibrium

What does this analysis of demand and supply indicate about the per unit price of blood products observed in the market? To answer this question, it is necessary to combine

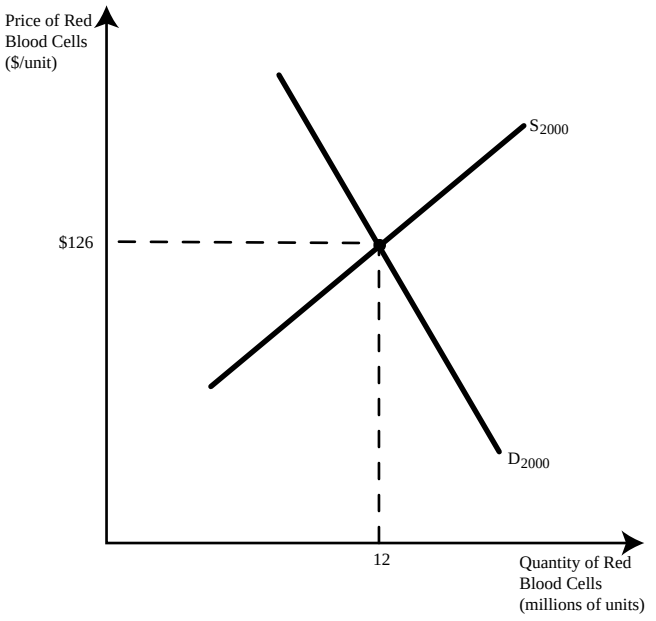


Figure 2.2 Equilibrium in the U.S. market for red blood cells in 2000. The point of intersection of the downward sloping demand curve (D_{2000}) and upward sloping supply curve (S_{2000}) represents the market outcome or equilibrium. In 2000, the average price charged by blood centers for red blood cells was $126 per unit in the U.S. The associated volume of red blood cells purchased by health care organizations was 12 million units.

the two sides of the market together, since it is the interaction of buyers and sellers in the marketplace that determines the outcome of a particular market. The per unit price that prevails in the market, along with the associated volume of blood that is bought and sold, is referred to as the market equilibrium. By definition, the market equilibrium price is the price at which the quantity of blood products buyers are willing and able to purchase is equal to the quantity of blood products sellers are willing and able to supply. Figure 2.2, for instance, illustrates the equilibrium price and quantity in the market for red blood cells in the U.S. in 2000. In particular, the average fee charged by blood centers in 2000 for red blood cells was $126 per unit, and the volume of red blood cells purchased was approximately 12 million units. Note that Figure 2.2 is a stylized representation of the U.S. blood market under competitive market assumptions (i.e., many small market participants, no product differentiation, and full information). If each community blood center is considered to be an individual seller, these conditions are largely met. As such, Figure 2.2 provides a simplified framework for illustrating general trends in the market.

To understand why a unit price of $126 and a volume of 12 million units is the market outcome in Figure 2.2, it is helpful to consider what would happen in the market if the price rises above or falls below $126. Suppose for example, that the market price is $150. At this price, the quantity of blood supplied exceeds that quantity of blood demanded, i.e., there is a surplus of blood in the market, as illustrated in Figure 2.3. In the face of a prolonged surplus, suppliers typically respond by decreasing the selling price in order to reduce their inventory. This reduction in price leads to an increase in quantity demanded and a decrease in quantity supplied, shrinking the surplus in the market. This downward pressure on the price continues until the equilibrium price of $126 is reached.

Now, consider what happens if the price falls below $126. At a price of $100, for example, the quantity of blood demanded exceeds the quantity of blood supplied, i.e., there is a shortage of blood in the market, as illustrated in Figure 2.3. This shortage puts upward pressure on the price of blood, as suppliers recognize their ability to increase price as a way of rationing the scarce blood. This increase in price leads to a decrease in quantity demanded and an increase in quantity supplied, reducing the size of the shortage, and continues until the equilibrium price of $126 is reached.

Thus, another way of thinking of the equilibrium price in a market is as the market clearing price. This is the price expected to emerge as prices adjust over time in a free market environment. The presence of an equilibrium price, however, does not mean that prices are constant in the long run. Since the equilibrium price is determined by the point of intersection of the demand and supply curve, if these curves shift or change over time, which they are likely to do, a new equilibrium price will emerge. This fact is illustrated in Figures 2.4 through 2.6, which clearly document the increasing (equilibrium) price of blood in the U.S. To understand this trend, it is necessary to examine more closely those factors affecting the position of the demand and supply curves in the U.S. in recent years.

Changes in Market Equilibrium

In general, an increase in the equilibrium price in a market can be triggered by a shift to the right of a demand curve (i.e., increase in overall demand) and/or a shift to the left of a supply curve (i.e., decrease in overall supply). Either of these shifts results in the point of intersection of the demand and supply curves being at a higher price. What is interesting to note is that the U.S. blood market has simultaneously experienced both an increase in demand and a decrease in supply in recent years. The result has been substantially higher blood prices.

Blood demand increased by 27% from 1994 to 2001 and is estimated to be increasing by 3% to 5% a year (5). The increase in blood demand is due in part to an aging population that consumes more health care. Since most health care is consumed toward the end of life, it should not be surprising that 46% of blood transfusions are to Medicare beneficiaries (6). Another significant factor in the demand for blood products has been the development of technological advancements in medicine and surgery. Complex procedures, previously unavailable, are now common. These

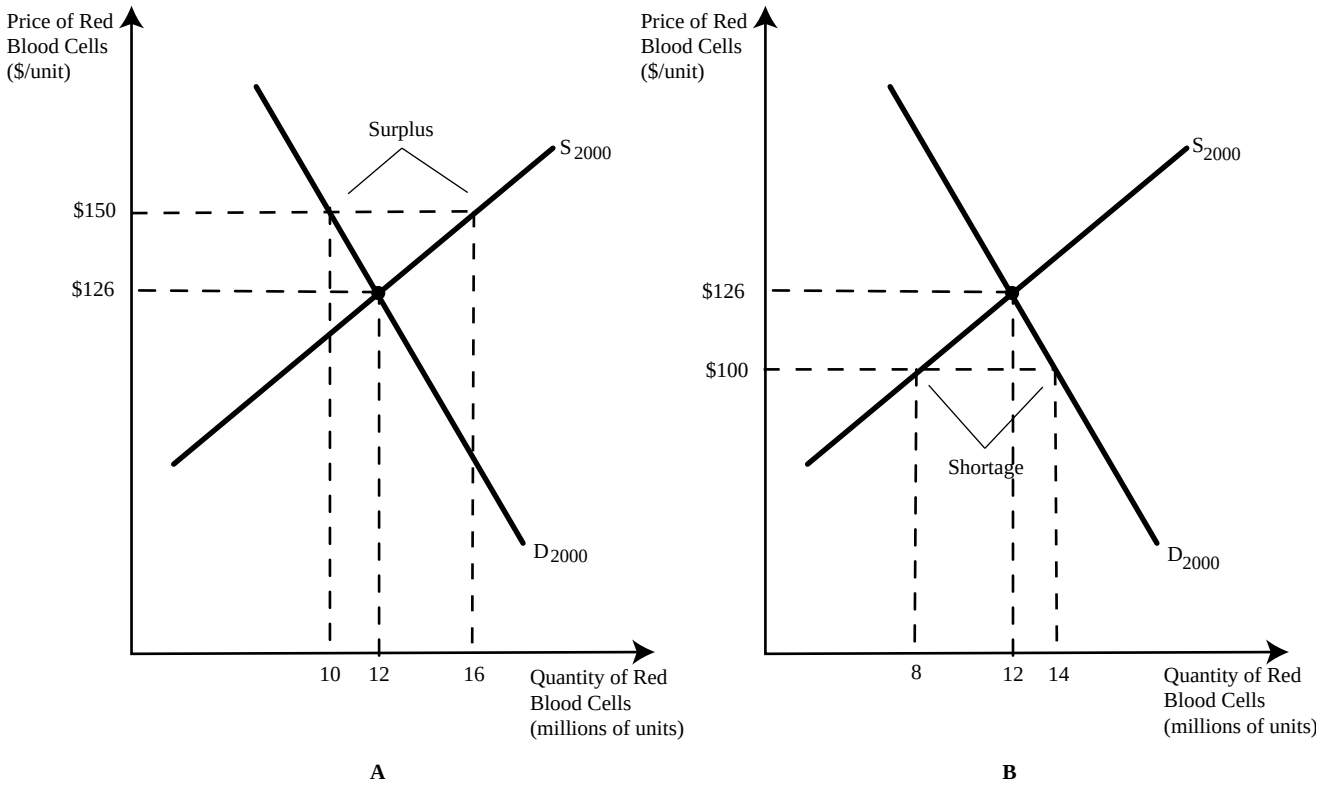


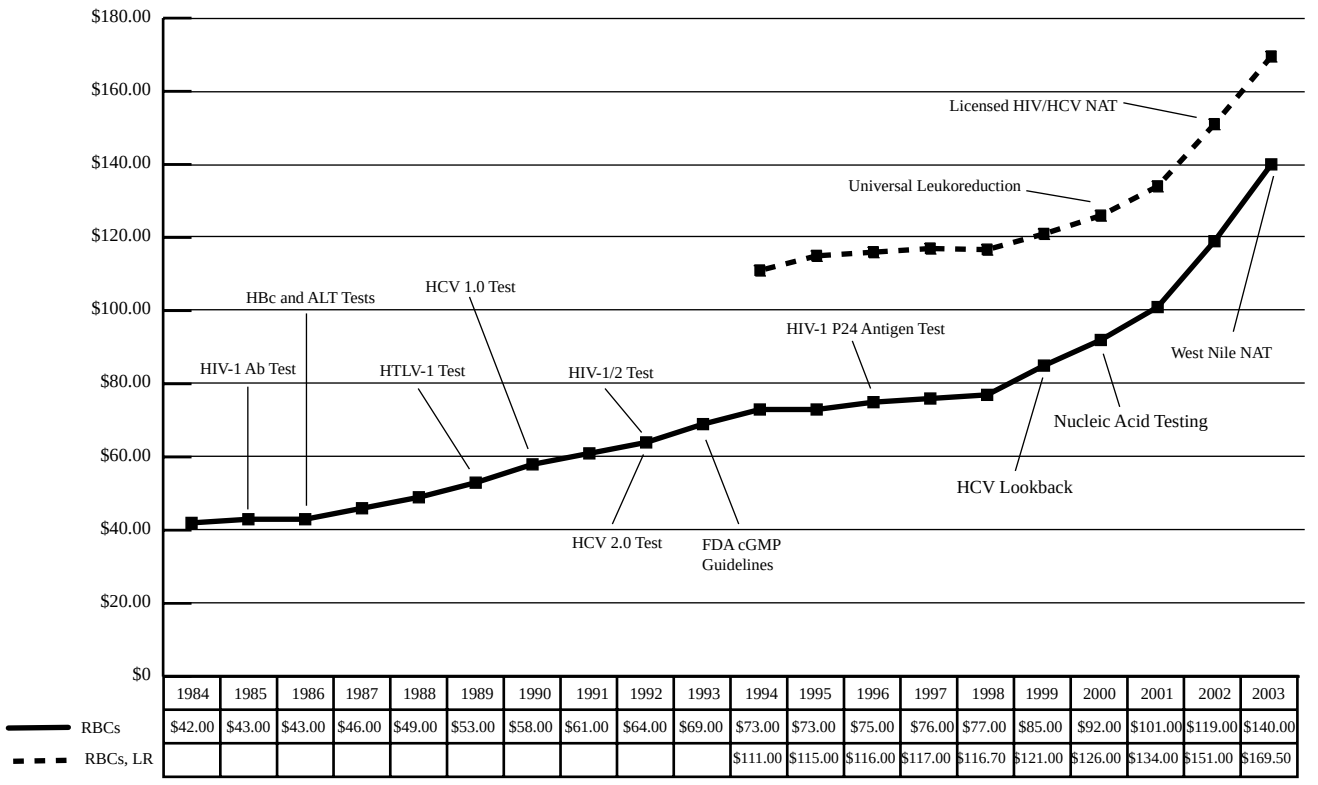
Figure 2.3 Conditions under which the U.S. market for red blood cells is not in equilibrium. If the market price ($150) is above the equilibrium price ($126), the quantity of red blood cells supplied (16 million units) exceeds the quantity of red blood cells demanded (10 million units). This is called a surplus **(A)**. When this occurs, sellers try to reduce inventory by decreasing the per unit price of red blood cells. As the price decreases, there is a decrease in quantity supplied and an increase in quantity demanded as the market adjusts to its equilibrium price. If the market price ($100) is below the equilibrium price ($126), the quantity of red blood cells demanded (14 million units) exceeds the quantity of red blood cells supplied (8 million units). This is called a shortage **(B)**. When this occurs, sellers respond by increasing the per unit price of red blood cells. As the price increases, there is an increase in quantity supplied and a decrease in quantity demanded as the market adjusts to its equilibrium price.

procedures include revision and complicated operations in cardiac, orthopedic, and cancer surgery; organ transplants; and aggressive chemotherapy regimens. The development and ultimate success of these procedures has been dependent on the ready availability of large amounts of blood products required to perform them safely. The net effect of these factors has been greater demand for blood products and a shift to the right in the demand curve, as illustrated in Figure 2.7.

On the supply side of the blood market, sellers have been struggling to keep up with this increasing demand due to a combination of four factors. First, there has been a steady decline in the number of people willing to donate blood. It is estimated that although 60% of the population is eligible to donate, only 5% are blood donors (7). The second reason is a reduction in corporate support for blood drives. In the past it was common for employers to allow blood drives at their work sites, allowing their employees time off work to donate. This practice continues to decline as the emphasis shifts from corporate citizenship to productivity and corporate profits.

The third significant factor has been the impact of increased donor restrictions aimed at increasing blood safety. By excluding potentially infectious donors based on risk screening assessments, the number of eligible donors has declined substantially. The recent exclusion of blood donors who had previously lived in or traveled to Europe has had a significant impact on an already strained blood supply. In order to protect the blood supply against the potential transmission risk of variant Creutzfeldt-Jakob disease, the FDA implemented the following donor restrictions effective in May 2002, excluding potential donors who:

- Lived in Europe for 5 years or more between 1980 and the present.
- Visited or lived in the United Kingdom for a total of 3 months or more between 1980 and 1996.
- Received a blood transfusion in the UK between 1980 and the present.
- Served overseas in the military and their dependents, who spent time in military bases in northern Europe during 1980 and 1990, or southern Europe during 1980 and 1996, for 6 months or more (8).



	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
RBCs	$42.00	$43.00	$43.00	$46.00	$49.00	$53.00	$58.00	$61.00	$64.00	$69.00	$73.00	$73.00	$75.00	$76.00	$77.00	$85.00	$92.00	$101.00	$119.00	$140.00
RBCs, LR											$111.00	$115.00	$116.00	$117.00	$116.70	$121.00	$126.00	$134.00	$151.00	$169.50

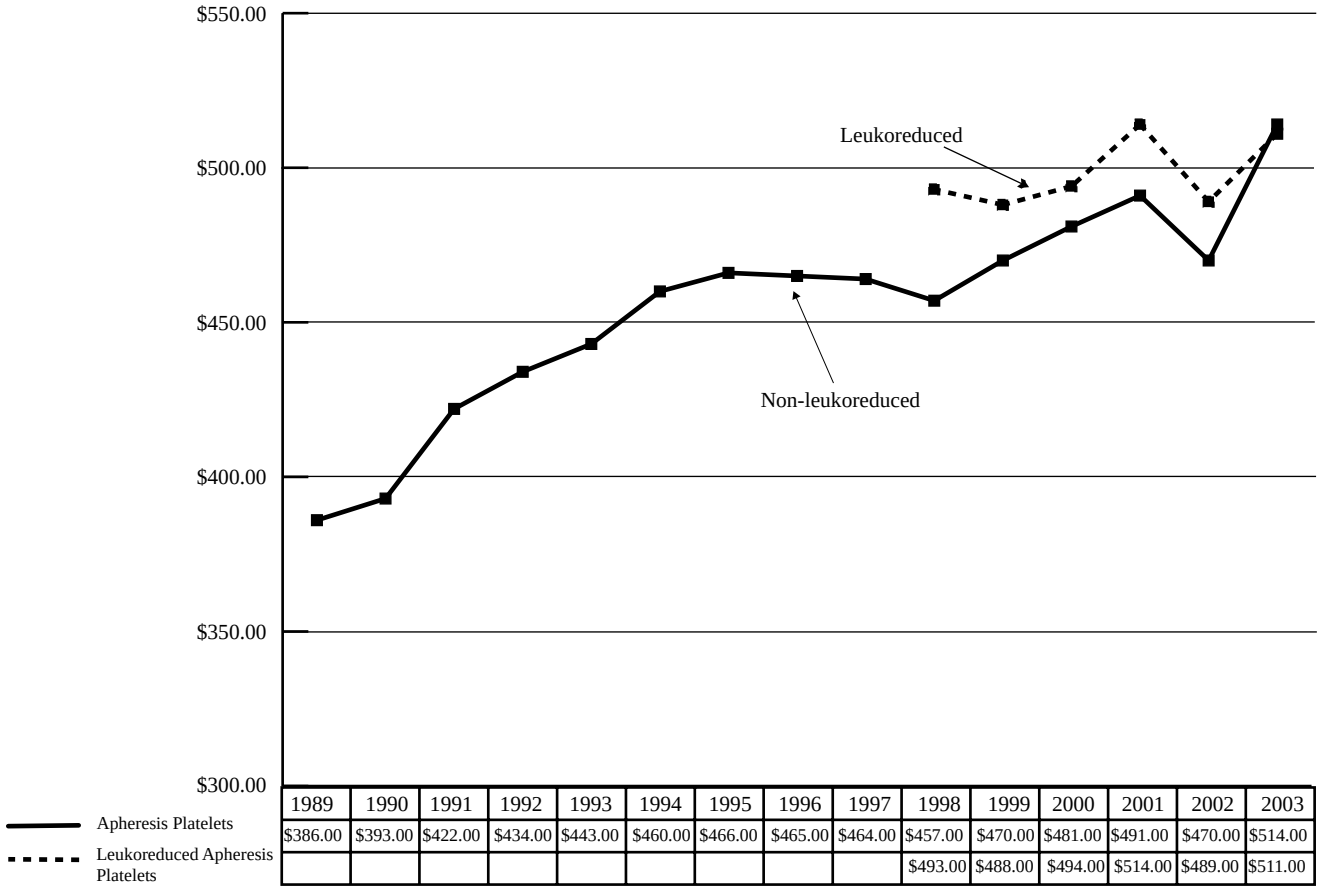
Figure 2.4 Safety measures and average red blood cell fees for the America's Blood Centers, 1984–2003. Adapted from Starkey, J., America's Blood Centers (written/oral communication). March 24, 2004.

The ultimate result of these deferrals may be as much as a 6% to 9% decrease in the blood supply and a shortfall of nearly one million units of blood (9).

The final factor contributing to the decrease in the U.S. blood supply is the increasing production costs faced by blood centers. Community blood centers affiliated with the American Red Cross (ARC) or America's Blood Centers (ABC) collect the majority of the U.S. blood supply (93%), with the remainder being collected by hospitals (1). Blood centers have seen steady increases in the cost of producing blood products over the past 15 years, with double-digit percentage increases from 1996 to 2000 (6). These cost increases have generally paralleled increases in safety and screening technologies that have been either mandated or recommended by regulatory agencies such as the FDA and the Department of Health and Human Services. Blood centers have also seen significant cost increases in other areas. In a highly regulated and high profile industry, blood processing centers have seen increasing costs associated with regulatory compliance and liability. Labor and overhead costs have also risen sharply because of the general increase in demand for, and declining supply of, laboratory medical technologists. Another source of cost increases has been the rising cost of donor recruitment. Of particular concern is the cost of donor replacement for those donors excluded by new safety screening requirements. When donation levels drop, additional resources are required for staffing recruitment drives and media campaigns.

The net effect of the four supply-side factors discussed above has been a decrease in the overall supply of blood. In other words, there has been a shift to the left in the supply curve. Combined with the shift in the demand curve to the right, the end result has been a greater threat of intermittent blood shortages in the short run and, eventually, further escalations in blood prices in the long run as the market adjusts to its new equilibrium, as illustrated in Figure 2.7. In 2000, the blood market is in equilibrium at a price of $126 per unit. After 2000, the market demand curve increases from D_{2000} to D_{2003} and the market supply curve decreases from S_{2000} to S_{2003}. Note that at the price of $126 per unit, a shortage now exists in the market, in that quantity demanded (Q_D) now exceeds quantity supplied (Q_S) at that price. As a result of this shortage, there is upward pressure on the market price. The point of intersection of the new demand curve in 2003 (D_{2003}) and the new supply curve in 2003 (S_{2003}) determines the new, higher equilibrium price of $169.50 per unit.

It is important to note that the market adjustment process has not typically proceeded in a smooth and uniform manner. Blood product price increases have been uneven and, at times, sudden. In July 2001, for example, the American Red Cross raised prices for blood products by 10% to 35%, citing substantial investments to comply with increased regulatory requirements and voluntary industry



	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Apheresis Platelets	$386.00	$393.00	$422.00	$434.00	$443.00	$460.00	$466.00	$465.00	$464.00	$457.00	$470.00	$481.00	$491.00	$470.00	$514.00
Leukoreduced Apheresis Platelets										$493.00	$488.00	$494.00	$514.00	$489.00	$511.00

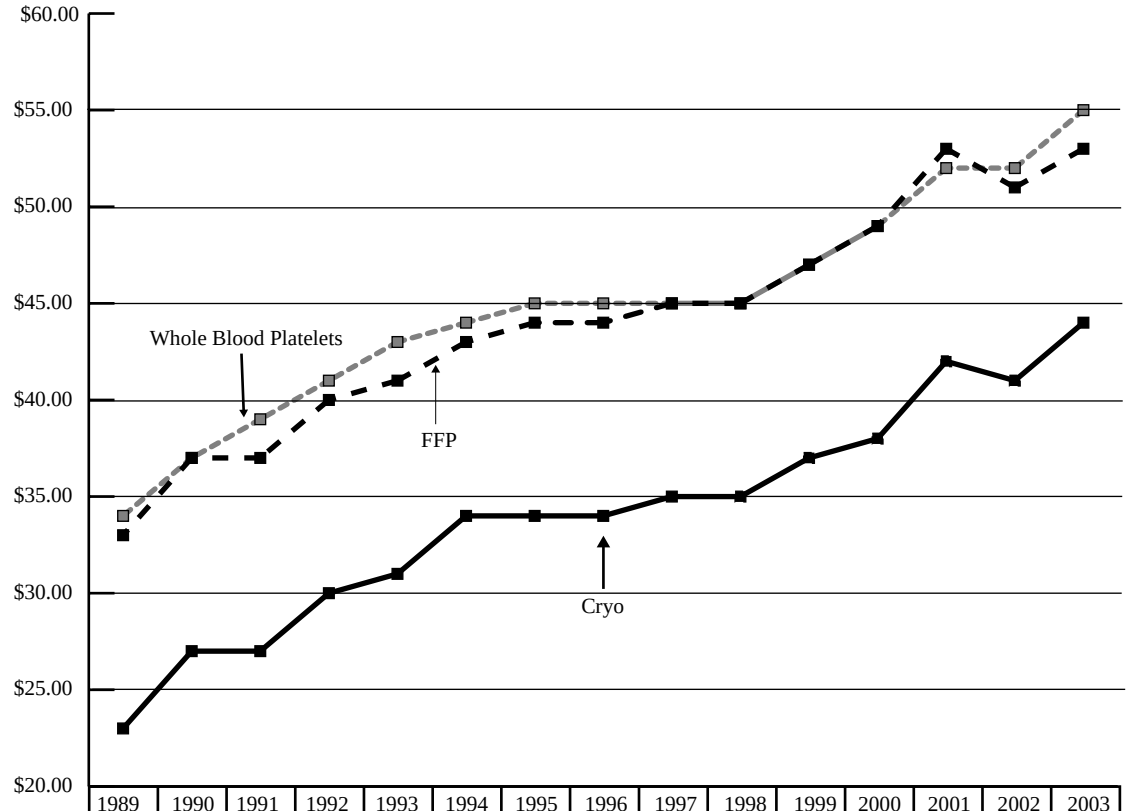
Figure 2.5 Average apheresis platelet fees for the America's Blood Centers, 1989–2003. Adapted from Starkey, J., America's Blood Centers (written/oral communication). March 24, 2004.

standards for viral screening technologies, and blood safety measures such as leukoreduction (6). A contributing factor to the sluggish nature of price changes in this market is the nonprofit status of the community blood centers. Because of this status, blood centers typically operate on a cost recovery basis and also receive partial funding from external sources, such that the prices they charge to hospitals may not immediately reflect increases in production costs. Interestingly, in some regions served by more than one blood center there has even been price competition among these nonprofit organizations (6). Ultimately, however, the increased costs of producing blood products must be passed on to client hospitals.

Comparing recent events in the blood market to prevailing conditions in the world oil market, it is now clear why both markets appear to be moving in tandem, but at different rates, in terms of prices (Fig. 2.1). As stated above, the increasing prices in the U.S. blood market are a result of a positive demand-side shock and a negative supply-side shock. Both market shocks have the same effect on price, i.e., they increase price. In contrast, in the world oil market, although demand is increasing, supply is not decreasing. Instead, world oil supply is merely constrained in the short run to be relatively constant, as it takes time and substantial resources to significantly increase oil capacity via new oil fields. Thus, world oil prices are increasing primarily as a result of a positive demand-side shock. Since there is no accompanying negative supply-side shock, upward pressure on price exists but is not as pronounced as in the U.S. blood market.

Elasticity of Demand

The magnitude of the increase in blood prices is affected not only by the size of shifts in the demand and supply curves, but by the shape of curves as well. In particular, the sensitivity of buyers to changing prices, reflected in the slope of the demand curve, influences the degree to which a given shift in a curve translates into higher prices. Economists use the term *price elasticity of demand* to refer to how sensitive consumers are to price changes in a particular product. The degree of price elasticity is influenced by a number of factors, including the availability of close substitutes, whether the product is a necessity or luxury, the proportion of budget spent on the product, and the time horizon for making a purchase decision.



	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Fresh Frozen Plasma	$33.00	$37.00	$37.00	$40.00	$41.00	$43.00	$44.00	$44.00	$45.00	$45.00	$47.00	$49.00	$53.00	$51.00	$53.00
Cryoprecipitated AHF	$23.00	$27.00	$27.00	$30.00	$31.00	$34.00	$34.00	$34.00	$35.00	$35.00	$37.00	$38.00	$42.00	$41.00	$44.00
Random Platelets	$34.00	$37.00	$39.00	$41.00	$43.00	$44.00	$45.00	$45.00	$45.00	$45.00	$47.00	$49.00	$52.00	$52.00	$55.00

Figure 2.6 Average fees for fresh frozen plasma, cryoprecipitate, and whole blood platelet units for the America's Blood Centers, 1989–2003. Adapted from Starkey, J., America's Blood Centers (written/oral communication). March 24, 2004.

In general, products that have a large number of available substitutes, do not require immediate purchase, or make up a relatively large proportion of the purchaser's budget are characterized as having more *elastic demand*. For these products, consumers have the ability and time to compare different products before making a purchase decision. Under these conditions, consumers are fairly sensitive to changes in the price of a product, which translates into a relatively flat demand curve (D_1), as illustrated in Figure 2.8. For a given change in price from P_1 to P_2, there is a relatively large change in quantity demanded from Q_1 to Q_3. Examples of products characterized as having elastic demand include fresh tomatoes, Toyota automobiles, and Coca-Cola.

In contrast, products that have few available substitutes, require immediate purchase, or make up a relatively small proportion of the purchaser's budget are characterized as having more *inelastic demand*. When demand is inelastic, consumers typically feel that they have fewer choices or options available to them and are either unable or unwilling to shop around. Under these conditions, consumers are fairly insensitive to changes in the price of a product, which translates into a relatively steep demand curve (D_2), as illustrated by in Figure 2.8. For a given change in price from P_1 to P_2, there is a relatively small change in quantity demanded from Q_1 to Q_2. Examples of products characterized as having inelastic demand include coffee, gasoline, and health insurance.

In the case of blood, demand is generally characterized as being price inelastic. In other words, blood is typically thought of as a necessity, needed on demand, with few available substitutes. Thus, the demand curve is relatively steep. As a result, any change in market equilibrium brought about by a shift in the demand and/or supply curve will be reflected primarily as a price change as opposed to a quantity change. Figure 2.9 illustrates this point for the case of a decrease in supply. As the supply curve shifts from S_1 to S_2, the equilibrium price in the case of elastic demand (D_1) increases from P_1 to P_2. When demand is relatively inelastic (D_2), this same shift in supply translates into an increase in the equilibrium price from P_1 to P_3.

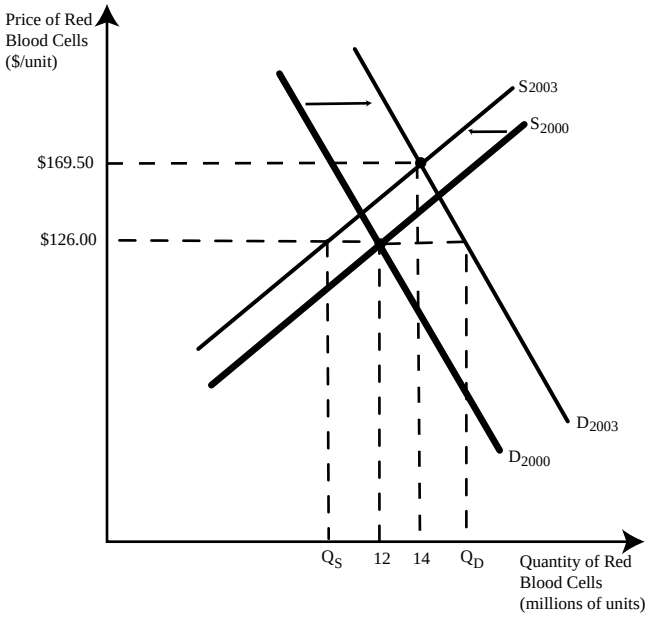


Figure 2.7 Changes in the U.S. market for red blood cells equilibrium between 2000 and 2003. The point of intersection of D_{2000} and S_{2000} represents the equilibrium price in 2000 ($126.00). Between 2000 and 2003, the market experienced an increase in demand (i.e., demand curve shifts from D_{2000} to D_{2003}) and a decrease in supply (i.e., supply curve shifts from S_{2000} to S_{2003}). In the short run, the equilibrium price does not change, leading to a shortage in the market at $126, as the new quantity demanded (Q_D) now exceeds the new quantity supplied (Q_S). This shortage puts upward pressure on prices, leading to a new equilibrium price. The point of intersection of D_{2003} and S_{2003} represents the new equilibrium price in 2003 ($169.50).

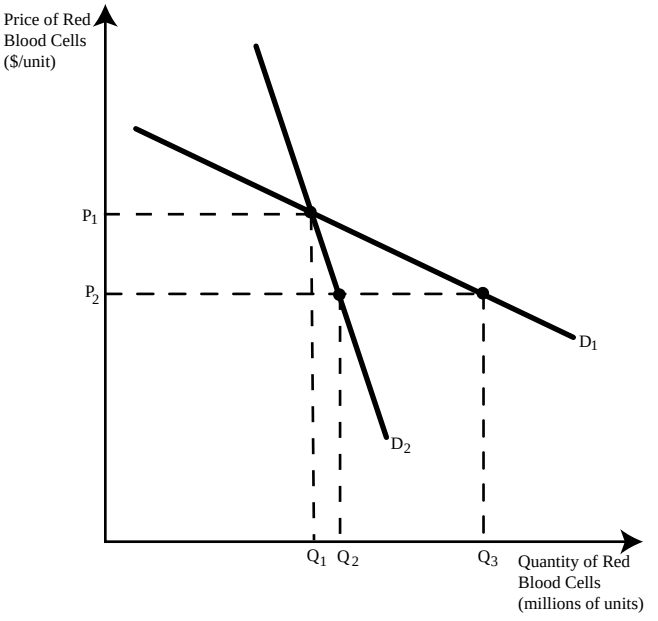


Figure 2.8 Elastic versus inelastic demand. If buyers are relatively sensitive to price, demand is said to be price elastic and the market demand curve is relatively flat (D_1). Under this condition, a given change in price (P_1 to P_2) results in a relatively large change in quantity demanded (Q_1 to Q_3). In contrast, if buyers are relatively insensitive to price, demand is said to be price inelastic and the market demand curve is relatively steep (D_2). Under this condition, the same change in price results in a relatively small change in quantity demanded (Q_1 to Q_2).

A wide variety of options currently exist to reduce the need for blood products, suggesting that the demand for blood may become more price elastic in the future. Alternatives to blood transfusion include recycling of blood in the operating room, anesthetic and surgical techniques, topical agents and drugs that reduce bleeding, hormones that stimulate blood cell production, and improved utilization by the use of more conservative transfusion practices. Despite the emergence of these viable substitutes, however, demand remains price inelastic. The key to this apparent discrepancy between economic theory and reality may be partially attributed to health care professionals' perception of these alternatives and their consequent level of use. The reasons for the apparent underutilization of these therapies include a general lack of emphasis and incentives for blood conservation measures, and misperceptions about the availability and relative costs of suitable transfusion alternatives. The economics of these transfusion alternatives will be discussed later in the chapter.

In summary, the increasing prices and intermittent shortages observed in the U.S. blood market can be attributed to a steep demand curve (i.e., relatively inelastic demand) that is increasing (i.e., shifting to the right) in conjunction with a declining blood supply (i.e., supply

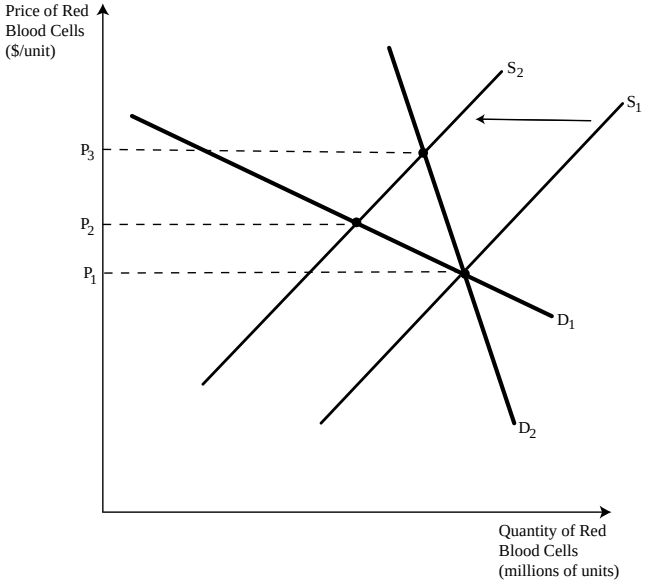


Figure 2.9 Relationship between elasticity of demand and equilibrium price changes. If buyers are relatively sensitive to price, demand is said to be price elastic and the market demand curve is relatively flat (D_1). Under this condition, a decrease in supply (i.e., shift from S_1 to S_2) will have a relatively small impact on equilibrium price (i.e., increase from P_1 to P_2). In contrast, if buyers are relatively insensitive to price, demand is said to be price inelastic and the market demand curve is relatively steep (D_2). Under this condition, the same decrease in supply will have a much greater impact on equilibrium price (i.e., increase from P_1 to P_3).

curve shifting to the left). Each factor alone has the potential to put upward pressure on the price of blood products. In combination, the impact is substantial.

Potential Remedies for Increasing Prices

Based on the demand-and-supply diagram of the blood market, there are two potential ways to reverse the upward trend of the price of blood products. In particular, a decrease in the equilibrium price can be brought about by a shift to the left of a demand curve (i.e., decrease in overall demand) and/or a shift to the right of a supply curve (i.e., increase in overall supply). Either of these shifts results in the point of intersection of the demand and supply curves being at a lower price. At the federal level, efforts to control the price of blood products and reduce potential shortages have centered on the supply side of the market. For example, a recent Congressional research report includes the following recommendations to fight the growing crisis in the blood market: improve donor recruitment, increase donations from existing donors, and eliminate specific donor restrictions (10). While such actions certainly have the potential to increase the blood supply and, thus, lead to lower prices in the blood market, they may be difficult and costly to implement given the current social, political, and economic climate.

The other potential means of fighting increasing prices is to focus on the demand side of the market. Although population demographics cannot be changed, what is controllable is the type and frequency of medical procedures and techniques used in health care organizations. Viable transfusion alternatives exist in many circumstances. Again, convincing health care practitioners to use these alternatives may be challenging, as implementing any type of organizational change is typically a complex and difficult task. Increasing blood product prices is not the only motivation for a more careful analysis of transfusion alternatives, however. The per unit price of blood products is only a small part of the total cost of transfusions. In the next section, the other components of transfusion costs are explored.

THE TOTAL COST OF TRANSFUSIONS

Direct Costs of Transfusions

The cost of actually transfusing blood products to patients is substantially more than just the cost of purchasing blood products from collection centers. The process of storing, testing, regulating, and transfusing blood products is tremendously complex and results in the consumption of a number of increasingly scarce and expensive hospital resources. These include laboratory and ward supplies and equipment, significant amounts of technician, nursing and supervisory labor, as well as administrative overhead. The consumption of these resources leads to transfusion costs that can be three to five times the cost of simply acquiring the blood products. Several studies, using different accounting techniques, have attempted to quantify the total cost of transfusing blood by accounting for direct materials, labor, and overhead. These studies, discussed below, are summarized in (Table 2.1). Note that Table 2.1 reports transfusion costs in terms of constant 2003 dollars, in order to control for the year in which the study was conducted.

Forbes et al. published the results of a 1988 survey of blood associated charges for 19 teaching hospitals (11). The hospitals were all Level I or Level II trauma centers, and the survey population included all patients that received blood products. Total costs of transfusion were

TABLE 2.1
PUBLISHED STUDIES ON ESTIMATED RBC COSTS IN 2003 DOLLARS

Author, Year	Facilities	Study Technique	Acquisition Cost (%)	Patient Sample	Cost/Unit (2003 $)[a]
Forbes, 1991	19 Teaching hospitals with level I or II trauma	Survey of blood related charges	37%	Mixed population	$386
Mohandas, 1995	Outpatient cancer center	Review of blood related charges for 219 patients	26%	Solid tumors Hematologic tumors	$629 $678
Cantor, 1998	Outpatient cancer center	Survey of blood related cost activities	15%	Solid tumors Hematologic tumors	$488 $500
Crémieux, 2000	Outpatient cancer center	Cost activities recorded for 517 patients	19%	Solid tumors Hematologic tumors Complex patients	$646 $684 $717

[a]Calculations based on the Consumer Price Index (CPI) for Medical Care Services. Adapted from Forbes JM, Anderson MD, Anderson GF, et al. Blood transfusion costs: a multicenter study. *Transfusion.* 1991;31:318–323; Mohandas K, Aledort L. Transfusion requirements, risks, and costs for patients with malignancy. *Transfusion.* 1995;35:427–430; Cantor SB, Hudson DV Jr., Lichtiger B, et al. Costs of blood transfusion: a process-flow analysis. *J Clin Oncol.* 1998;16:2364–2370; Crémieux PY, Barrett B, Anderson K, et al. Cost of outpatient blood transfusion in cancer patients. *J Clin Oncol.* 2000;18:2755–2761.

estimated by examining hospital charges for blood acquisition and blood related activities. These activities included handling charges, laboratory charges, and blood administration charges. Blood costs were then calculated using the hospital's Medicare cost-to-charge discount ratio to estimate the actual hospital cost from the patient charges. From this data, the average hospital cost of one unit of red blood cells was $155 in 1988 dollars. Blood related activities accounted for the majority of this blood cost; only 37% of the total cost was attributed to acquisition costs. There were several limitations of this study's ability to capture total blood costs. The ability to extrapolate costs from charges is limited by how accurately each hospital accounts for the actual cost of goods and services it provides. These costs must capture the cost of direct materials, fixed and variable labor costs of providing the services, as well as an accounting for overhead, such as equipment costs, facility maintenance, supervision, and administrative support. A comprehensive review of hospital blood coding practices and hospital charges noted systemic problems in accurately capturing and adequately billing for blood related costs (6). Further, no attempts were made in the survey to capture costs or include charges outside of the laboratory, such as the costs for ordering and actually transfusing the blood products to patients.

Mohandas and Aledort published a review of transfusion associated charges for 219 cancer patients at a single institution during the calendar year 1993 (12). Charts and billing records were reviewed to capture all blood and blood related charges. Significantly, the review included charges for blood administration and for transfusion aberrations, such as transfusion reactions and special laboratory studies. The reported average total cost of a red blood cell unit was $455 in 1993 dollars for lymphoma patients and $411 for solid tumor patients. Acquisition costs comprised 26% of total blood costs in these patients. This study had the same limitations as the one by Forbes et al. with regard to using charge data, although charges generated outside of the blood bank were included in the analysis. However, it appears that the charges were not discounted with a cost-to-charge ratio to arrive at actual hospital costs.

Cantor et al. published the results of a 1995 survey of blood costs at an outpatient cancer center (13). Unlike the previous studies, this study used a sophisticated activity-based accounting method to calculate actual costs, rather than extrapolating costs from hospital charges. A technique called process-flow analysis was used to map all activities and capture all relevant cost in the transfusion process, from blood ordering to administration and monitoring of the blood transfusion to the patient, as illustrated in Figure 2.10. Cost activities were categorized into three groups: direct variable, direct fixed, and indirect fixed. Direct variable costs are supplies and labor that are directly related to blood transfusions that vary with the level of output (units of blood transfused), such as the actual blood products, blood administration supplies, and test kits. Direct fixed costs are also related to the actual transfusion of blood products, but these costs do not vary with output, at least in the short run. These include labor for clinical and managerial personnel, and clinical facility costs in areas that are involved in blood storing, testing, processing, and administration. Indirect fixed costs include allocated expenses for supporting services, facility costs, and general administration. In addition to accounting for these resources and their costs, estimates were included for the additional cost of mild, moderate, and severe transfusion reactions with a frequency of 5.0%, 0.5%, and 0.04%, respectively. One of the striking results of this study was the total amount of clerical, nursing, and physician labor involved in the process of transfusing blood (Table 2.2). The total cost of transfusing blood products varied from $548 to $569 in 1995 dollars for a two-unit, red blood cell transfusion (Table 2.3). Acquisition costs comprised only 15% of the total transfusion costs.

Crémieux et al. also studied the cost of outpatient blood transfusions, reviewing activity and cost data for 517 cancer patients during the period 1995 and 1996 (14). Similar to Cantor et al., a process flow map was constructed and costs were grouped in four categories: direct material, variable direct labor, fixed direct labor, and overhead (Fig. 2.11). The total cost in 1998 dollars of transfusing a unit of red blood cells was determined to be $469 for adult patients and $568 for pediatric patients. The difference in costs between these two groups was largely due to the usual practice of transfusing one unit of blood to pediatric patients per visit as opposed to the typical two-unit transfusion to adults, such that fixed and overhead costs were distributed over less units of blood. Adult hematologic cancer patients and patients classified as complex had substantially

TABLE 2.2

SUMMARY OF DIRECT TIME OF PROFESSIONAL AND CLERICAL STAFF ASSIGNED TO NONEMERGENCY OUTPATIENT TRANSFUSION OF 2 UNITS OF ALLOGENEIC PACKED RBCS

Personnel	Time (minutes)
Charge nurses	32
Primary care nurses	95
Hospital aides	50
Clerical staff	60
Subspecialty physicians	25
Subspecialty nurses	15
Subspecialty clerical	15

Times do not include extra time for transfusion complications. Reprinted with permission from the American Society of Clinical Oncology. Adapted from Cantor SB, Hudson DV Jr, Lichtiger B, et al. Cost of blood transfusion: a process-flow analysis. *J Clin Oncol.* 1998;16(7):2367.

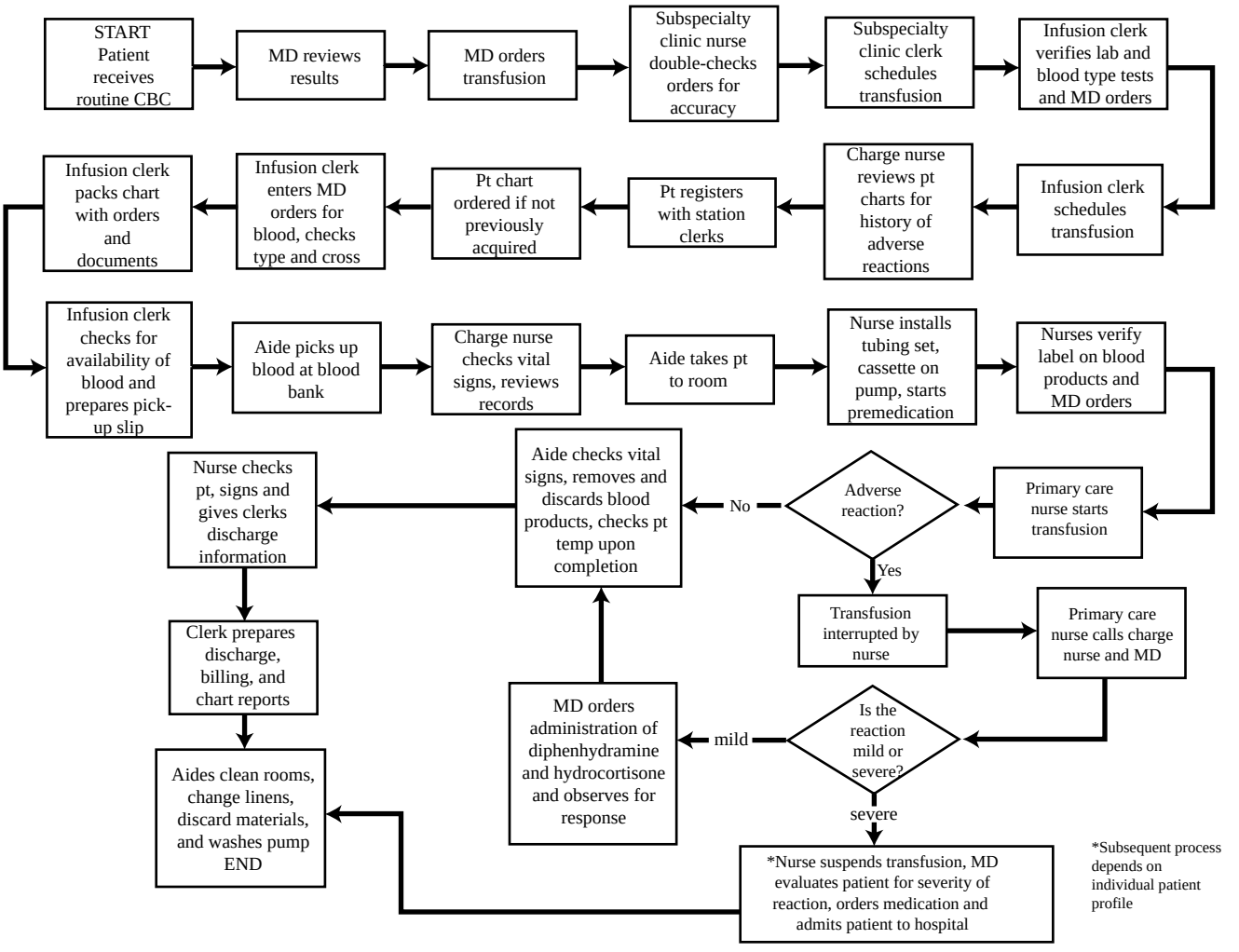


Figure 2.10 Process flow analysis of an outpatient transfusion, reflecting the multiple steps and resources involved in delivery of a blood transfusion. Reprinted with permission from the American Society of Clinical Oncology. Adapted from Cantor SB, Hudson DV Jr, Lichtiger B, et al. Cost of blood transfusion: a process-flow analysis. *J Clin Oncol*. 1998;16(7):2366.

higher average transfusion costs of $512 and $545, respectively. The increased costs in these patients were attributed to additional testing requirements, more transfusion reactions, and the more frequent use of specialized blood products, such as irradiated, washed, or CMV negative. Acquisition costs accounted for 19% of total transfusion costs in this study.

Despite similar patient populations and evaluation processes, the total cost of transfusing a unit of blood was substantially higher in the study by Crémieux et al. than in the study by Cantor et al. This difference may be attributed to a combination of factors, including regional variations in the cost of fixed assets and labor, substantial differences in blood acquisition costs, and an adjustment to 1998 dollars by Crémieux et al. but not Cantor et al. The study by Crémieux et al. may have also more accurately captured the cost of transfusion reactions since these were actual cost rather than estimates. The Crémieux et al. study also demonstrated substantial differences in transfusion costs for cancer patient based on age, tumor type, and clinical complexity (Table 2.1).

Indirect Costs of Transfusions

The previously noted studies demonstrate that transfusion costs are substantially more than blood costs when there is accounting for supplies, labor, and overhead. Three of the four studies also included an accounting for acute transfusion reactions, which range from mild to severe and can occur with a frequency of up to 6% of all transfusions (14). There are a variety of other adverse effects of transfusions, although their frequency has generally been decreasing due

TABLE 2.3
MEAN COST OF OUTPATIENT TRANSFUSION OF TWO UNITS OF ALLOGENEIC PACKED RBCS

Cost ($)	Non-BMT Solid Tumor	BMT Solid Tumor	Non-BMT Hematologic Malignancy	BMT Allogeneic Hematologic Malignancy	BMT Autologous Hematologic Malignancy
Direct Variable					
Personnel	98	118	118	118	118
Supplies	35	35	35	35	35
Blood (allogeneic)	80	80	80	80	80
Lab tests	33	32	34	34	32
Subtotal	246	266	268	268	266
Direct Fixed					
Facilities	35	35	35	35	35
Clinic	34	34	34	34	34
Subtotal	68	68	68	68	68
Indirect Fixed					
Blood/lab	151	149	151	151	150
General overhead	82	82	82	82	82
Subtotal	233	231	233	233	232
Total	$548	$565	$569	$569	$566

Reprinted with permission from the American Society of Clinical Oncology. Adapted from Cantor SB, Hudson DV Jr, Lichtiger B, et al. Cost of blood transfusion: a process-flow analysis. *J Clin Oncol.* 1998;16(7):2367.

to donor screening and pathogen detection technologies (Table 2.4). Transmission of viral agents is now an exceedingly small risk, with hepatitis B, hepatitis C, and HIV transmission estimated to occur in only 1:220,000, 1:1 million, and 1:2 million transfusions, respectively (15). The additional cost of these events is difficult to estimate since they occur with such a low frequency. Much more common are bacterial contamination of platelets, occurring with a frequency of 1:2000 platelet transfusions, and transfusion-related acute lung injury (TRALI), with an estimated frequency of 1:8000 transfusions (16,17). Both bacterial sepsis and TRALI can result in substantial morbidity and mortality, particularly in compromised or elderly patients. Again, the relatively low occurrence of these events would have minimal impact on the incremental cost per transfusion at the average community hospital.

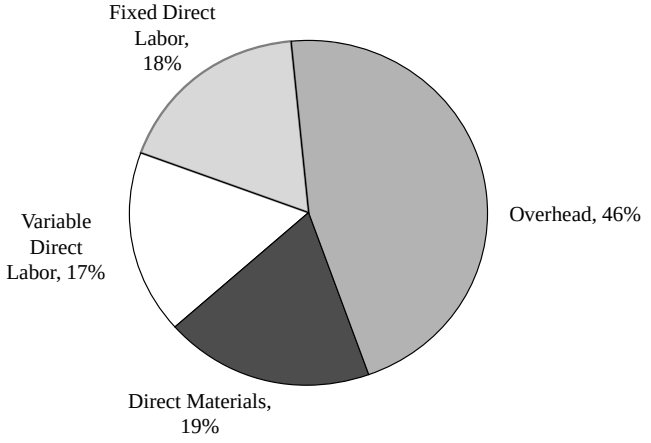


Figure 2.11 Transfusion costs by resource category. Direct material costs reflect the costs of acquiring blood products and supplies as a percentage of total cost. Reprinted with permission from the American Society of Clinical Oncology. Adapted from Crémieux PY, Barrett B, Anderson K, et al. Cost of outpatient blood transfusion in cancer patients. *J Clin Oncol.* 2000;18(14):2760.

From the perspective of resource consumption and economics, the greatest potential impact of blood transfusions is transfusion-related immunomodulation (TRIM). Allogeneic blood transfusions introduce a variety of foreign antigens that invoke immunologic changes in transfused patients. These immunological changes include both stimulation of humoral immunity resulting in alloantibody production and down regulation of cellular immunity resulting in altered host defenses (18). These immunologic changes may be beneficial to some patients but harmful to others. Decreased cellular immunity from transfusions can decrease organ transplant rejections and the severity of

TABLE 2.4
SOME ESTIMATED RISKS OF BLOOD TRANSFUSIONS

	Frequency of Occurrence Per Million Units (per actual unit)
Infectious Virus	
Hepatitis B	4 (1/220,000)
Hepatitis C	1 (1/800,000 − 1/1.6 x 10^6)
Human immunodeficiency	1 (1/1.4 − 2.4 x 10^6)
Bacteria	
Red cells	2 (1/500,000)
Platelets	500 (1/2,000)
Acute hemolytic transfusion reactions	1 to 4 (1/250,000 − 1,000,000)
Delayed hemolytic transfusion reactions	1,000 (1/1,000)
Transfusion-related acute lung injury	125 (1/8,000)

Reprinted with permission from Goodnough LT. Risks of blood transfusion. *Crit Care Med.* 2003;31:12(suppl):S679.

inflammatory diseases such as Crohn's disease, but this immunosuppression can also lead to adverse effects such as increased bacterial infections and decreased cancer survival (18–20). There has been considerable debate in the literature over the past decade about whether the observed relationship between allogeneic blood transfusions and adverse effects such as bacterial infections is cause and effect or merely correlation (15). However, evidence continues to mount that supports both the theory and existence of the clinical effects of TRIM.

Blumberg and Heal have suggested that three criteria should be met to prove causation of the immunosuppressive effects of blood transfusions (21). First, there should be a reproducible association between blood transfusions and adverse effects in cohort or epidemiologic studies, even after adjusting for confounding variables. Ideally, there should also be a dose-response relationship between this cause and effect. In fact, there are numerous studies that have shown blood transfusions to be independently associated with adverse clinical effects after using multivariate analysis to adjust for confounding factors, such as the effects of age, coexisting medical conditions, bleeding, anemia, and duration of surgery. These studies have shown an independent relationship between allogeneic blood transfusions and infection rates in orthopedics (22,23), cardiac surgery (24), spine surgery (25), trauma (26–29), colon surgery (30–32), and critical care patients (33,34). A recent meta-analysis reviewed 20 peer-reviewed articles that investigated the association between transfusion and postoperative bacterial infections (35). The total number of patients included in the meta-analysis was 13,152 and all studies had criteria for inclusion of a clearly defined control group (non-transfused) compared with a treatment group (transfused) using stepwise multivariate logistic regression analysis. All 20 studies demonstrated odds ratios that were greater than unity, with 17 of 20 reaching statistical significance. The common odds ratio for all studies was 3.5, and a subset of trauma studies had an odds ratio of 5:3 (35). An independent relationship between transfusions and multisystem organ failure has also been demonstrated in trauma patients (36), and transfusions are independently associated with higher mortality rates in cardiac surgery (37,38), trauma patients (29), and critical care patients (39,40). The most striking aspect about all of these studies, which cut across medical disciplines and describe a variety of outcomes, is the consistent finding of a dose-response relationship between the amount of blood products received and adverse effects (Fig. 2.12).

The second criterion proposed by Blumberg and Heal is that there should be a mechanistic explanation for the causal relationship between allogeneic transfusions and adverse clinical effects (21). A unifying theory that links immune mechanisms and outcomes has been proposed that relates to altered cellular immunity. Animal and human clinical studies have shown that allogeneic transfusions tend to down regulate cellular immunity by decreasing natural killer cell (NK) and macrophage activity, while causing activation of T-suppressor cells (18,19,25,41). Impaired cellular immunity would contribute to reduced allograft rejection and decreased inflammatory effects of clinical diseases such as Crohn's and rheumatoid arthritis, and would also account for increased infections and cancer recurrence rates. Most investigators believe these immune effects are primarily mediated by allogeneic white blood

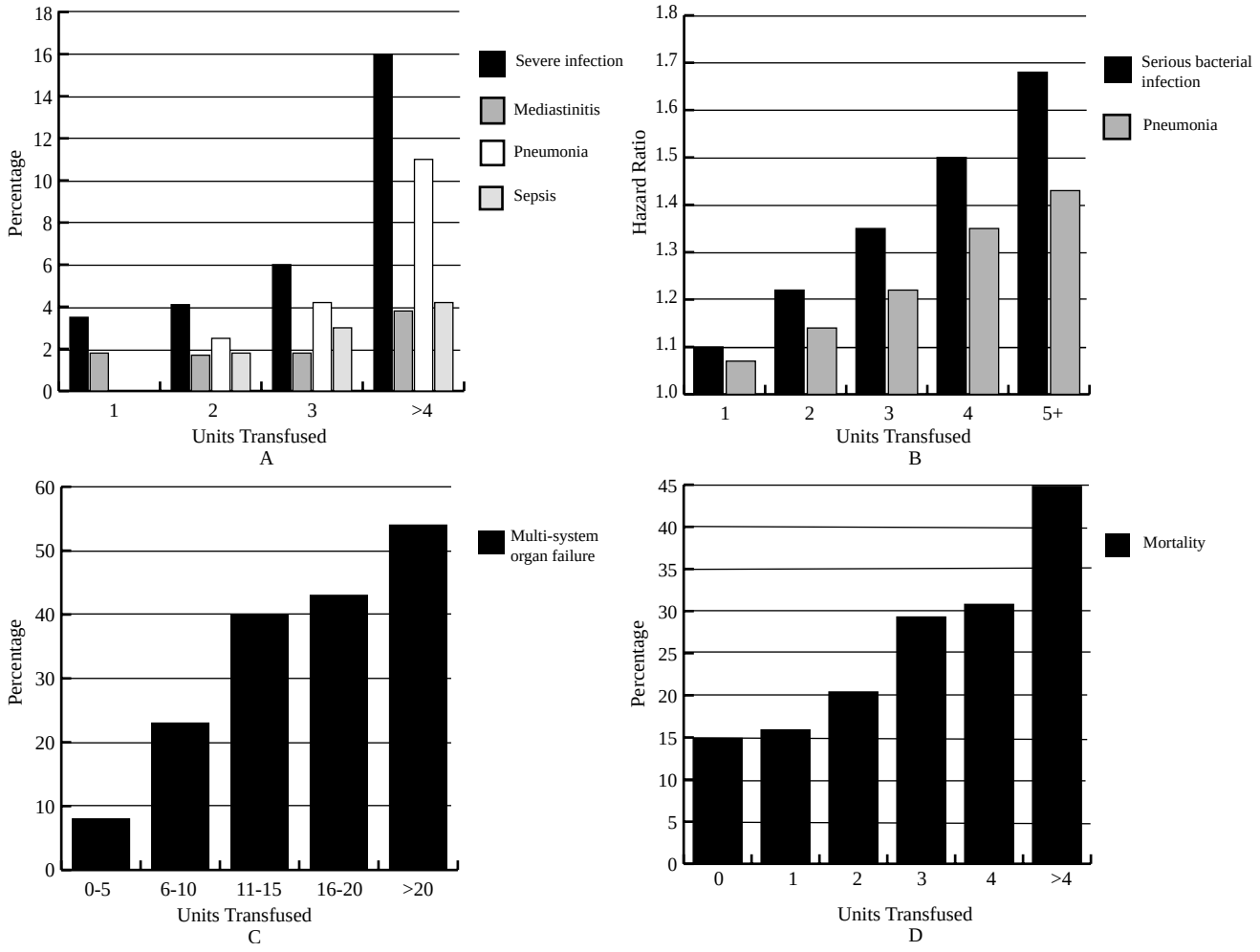


Figure 2.12 Dose-response relationships. Several studies have documented the relationship between number of units transfused and various clinical effects, including the dose-response relationship between units of blood transfused and severe postoperative infections in cardiac surgery **(A)**, serious postoperative bacterial infections and pneumonia in hip fracture patients **(B)**, multisystem organ failure in trauma patients **(C)**, and mortality in critical care patients **(D)**. Redrawn with permission from Leal-Noval SR, Rincon-Ferrari MD, Garcia-Curiel A, et al. Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. *Chest*. 2001;119(5):1466; redrawn with permission from Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogenic blood transfusion among patients undergoing hip fracture repair. *Transfusion*. 1999;39(7):698; redrawn with permission from Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Arch Surg*. 1997;132(6):622; redrawn with permission from Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients, *JAMA*. 2002;288(12):1504.

cells that are contaminants in red cell and platelet transfusions, although other foreign antigens and cytokines may also be involved (19,41,42).

The final criterion proposed by Blumberg and Heal is that altering or removing the causal factor of TRIM should lead to changes in outcomes (21). In support of this criteria, studies have shown that patients transfused with autologous blood have greatly reduced bacterial infections rates when compared to similar patients transfused with allogeneic blood (23,43,44). Transfusion of autologous blood would not present foreign white cells or antigens, so immunomodulation should not occur. Modification of allogeneic blood by leukoreduction has also been proposed as a method to reduce or eliminate the immunomodulatory effects of allogeneic transfusions. White blood cells are unintended contaminants of red blood cell and platelet units that have been separated from whole blood. Leukoreduction is an efficient filtration method that can greatly reduce the amount of these white cells. Several studies have concluded that leukoreduced blood products reduced

postoperative infection rates compared to non-leukoreduced transfusions (32,38,45–48), although other studies have not consistently demonstrated this reduction (49–55). However, there is evidence to support reduced morbidity, mortality, and length of stay using leukoreduced blood products (38,47,51,53,55). The economic issues of leukoreduction will be discussed later in the chapter.

In conclusion, the scientific evidence in support of immunomodulation by allogeneic blood products is compelling. Perhaps more compelling is the potential economic impact of TRIM. As previously discussed, the immunosuppressive effect of blood transfusions results in a dose-dependent increase in adverse clinical effects. These adverse clinical effects then lead to dose-dependent increases in ventilator times, ICU days, and total hospital days (29,39,40,56–58) (Fig. 2.13). In terms of economics, the dose-response relationship between the number of blood transfusions and adverse clinical effects also describes the relationship between blood transfusions and hospital resource consumption (Fig. 2.14). These resources include nursing and allied health labor, drugs, medical equipment and supplies, ventilators, laboratory tests, radiology studies, and hospital beds. In a review of 487 colorectal cancer patients, Vamvakas and Carven determined the slope of this resource consumption curve to be a 1.3% increase in length of stay and a 2% increase in hospital charges for every unit of red blood cells or platelets transfused (59). Blumberg et al. also attempted to define this relationship by reviewing hospital costs and charges of patients undergoing hip replacement surgery who received blood transfusions. The analysis demonstrated an incremental cost in 1992 dollars of $1043 to $1480 per unit of allogeneic blood transfused compared to patients who received either autologous blood or no blood products (43). Converted to 2003 dollars, this represents an additional cost incurred of $1600 to $2400 per unit of allogeneic blood transfused. This incremental cost likely reflected adverse effects of transfusions leading to increased resource consumption, since there were statistically significant increases in laboratory, pharmacy, and hospital room charges in transfused patients.

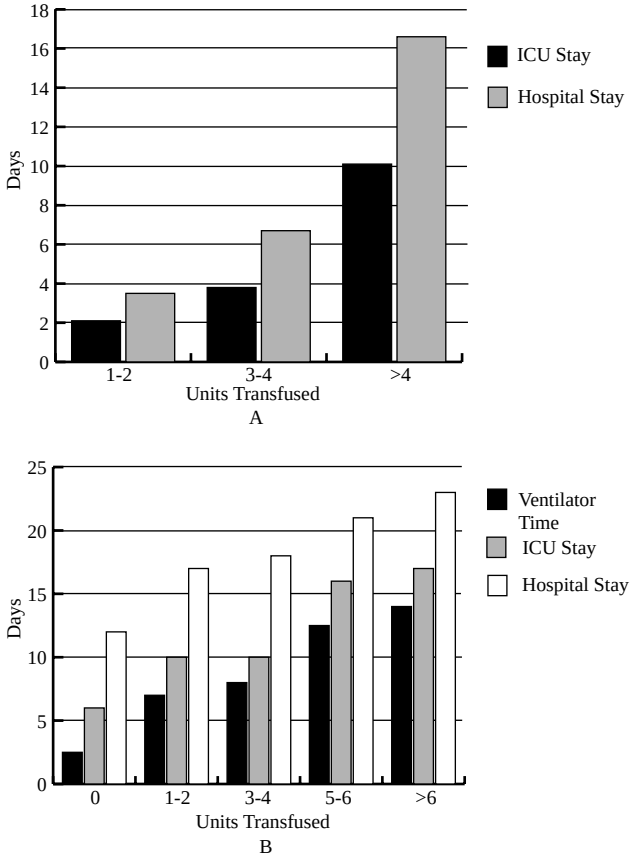


Figure 2.13 Relationship between length of stay and number of units transfused. There is a dose-response relationship between units of blood transfused and ICU and hospital length of stay in critical care patients **(A)** and ventilator time, ICU length of stay and hospital length of stay in trauma patients **(B)**. Redrawn with permission from Corwin HL, Gettinger A, Pearl RG, et al. *Crit Care Med.* 2004;32(1):42; redrawn with permission from Shapiro MJ, Gettinger A, Corwin HL, et al. Anemia and blood transfusion in trauma patients admitted to the intensive care unit. *J Trauma.* 2003;55(2):271.

It is particularly instructive to review the variable cost of hospital resources that have been shown to increase in transfused patients (Table 2.5; all costs normalized to 2003 dollars). Variable costs are those that are incurred on a per use or per event basis, such that they reflect incremental cost burden when they occur or cost savings if avoided. The association between blood transfusions and increased ventilator support and length of stay would add considerably to total transfusion costs incurred by hospitals. The cost of a postoperative hospital day is $1100 (60), the cost of an ICU day is $3200, which increased to $4400 a day if ventilator support is required (61). The incremental cost of a serious bacterial infection in an orthopedic patient is $16,600 to $17,900 (22,62), demonstrating the potential economic impact of the link between transfusions and postoperative infections. Bleeding complications can be particularly expensive in surgical patients, since bleeding can prolong operating room time and impact outcomes as well as postoperative length of stay. The variable cost per hour of operating room time is $1670 to $2750, such that even minor intraoperative delays to deal with bleeding can be quite costly (63). Even more costly is the impact of postoperative bleeding, particularly if it requires reoperation. Reoperation for bleeding in cardiac surgery patients has been shown to greatly increase postoperative morbidity and mortality (64,65), and has an incremental cost of $25,600 to $27,300 (60,66).

It should be evident from the previous discussions that the total cost of transfusing patients is substantially more than just the cost of blood acquisition. The cost of

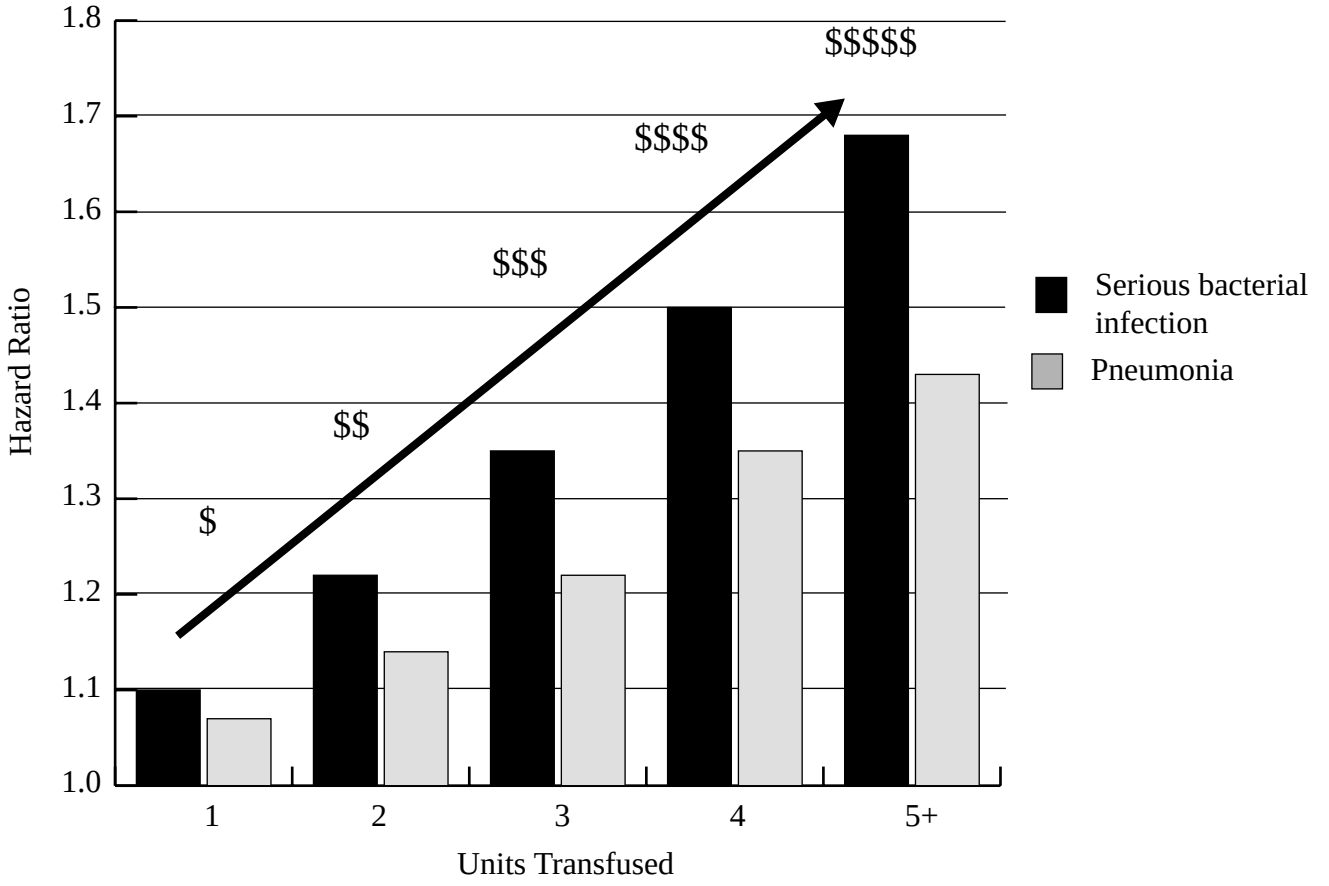


Figure 2.14 Economic dose-response relationship between units of blood transfused and consumption of hospital resources. Redrawn with permission from Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogenic blood transfusion among patients undergoing hip fracture repair. *Transfusion*. 1999;39(7):698.

purchasing blood products is merely the tip of the iceberg of total blood costs, when accounting for transfusion related supplies, labor, overhead, and potential adverse effects (Fig. 2.15). Of great importance to hospitals is the fact that the majority of these costs are incurred at the hospital level, such that they are potentially controllable. Hospitals cannot control the acquisition cost of blood products, but they do have control over local blood utilization policies and the use of transfusion alternatives. These issues will be discussed later in the chapter.

Opportunity Costs of Transfusions

A final area of blood costs are the opportunity costs associated with blood shortages, blood donations, and the short-term and long-term adverse effects of blood transfusions. For hospitals, there can be tremendous opportunity costs resulting from blood shortages. Local blood centers issue alerts to client hospitals when blood supplies fall below a critical level, asking the hospitals to curtail or cancel elective surgeries that may require blood products. For hospitals, these elective surgeries are often the primary source of income to improve their operating margins. Surgery cancellations not only deny hospitals this revenue, but also cause them to lose costs associated with idle operating rooms and personnel. Opportunity costs that should also be considered are those incurred by donors and patients. The process of blood donation can take several hours and in many cases a visit for an outpatient blood transfusion can take an entire day; consequently, opportunity costs for employees and employers can be substantial. Two recent studies attempted to capture the societal costs of blood donations and blood transfusions in the United Kingdom and in Canada (67,68). The opportunity cost incurred by blood donors was estimated to be $28 per unit, reflecting lost wages, transportation costs, and the indirect costs of lost productivity. The UK study also attempted to account for the costs associated with increased length of stay and adverse effects of transfusions, which were estimated to be $570 per unit of blood transfused (67). Extrapolating these costs to the U.S. which collects 14 million units of whole blood and transfuses 27 million units of blood products annually, the opportunity cost to blood donors would

TABLE 2.5

HOSPITAL RESOURCE VARIABLE COSTS, NORMALIZED TO 2003 DOLLARS

Hospital Resource	Variable Cost (2003$)[a]
Operating room variable time	$1670–$2750/hour
Postoperative hospital day	$1100/day
ICU day	$3200/day
ICU day—ventilated patient	$4400/day
Serious postoperative infection—orthopedic surgery patient	$16,600–$17,900
Reoperation for bleeding—cardiac surgery patient	$25,600–$27,300
[§]Red blood cell transfusion—variable cost per unit	$1600–$2400/ unit

Variable costs are those that are incurred on a per use or per event basis, such that they reflect the potential for incremental cost burden or cost savings.
[a]Calculations based on the Consumer Price Index (CPI) for Medical Care Services. Adapted from Carson JL, Altman DG, Duff A, et al. Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. *Transfusion.* 1999;39:694–700; Blumberg N, Kirkley SA, Heal JM. A cost an alysis of autologous and allogeneic transfusions in hip-replacement surgery. *Am J Surg.* 1996;171:324–330; Engoren M, Arslanian-Engoren C, Steckel D, et al. Cost, outcome, and functional status in octogenarians and septuagenarians after cardiac surgery. *Chest.* 2002;122:1309–1315; Roberts CS, Dasta JF, Klim SR, et al. Factors affecting the cost of an intensive care unit (ICU) day: implications for pharmacoeconomic studies. Paper presented at: American College of Clinical Pharmacy Annual Meeting; November Day(s), 2003; Atlanta, Ga.; Sonnenberg FA, Gregory P, Yomtovian R, et al. The cost-effectiveness of autologous transfusion revisited: implications of an increased risk of bacterial infection with allogeneic transfusion. *Transfusion (Paris).* 1999;39:808–817; Dexter F, Blake JT, Penning DH, et al. Use of linear programming to estimate impact of changes in a hospital's operating room time allocation on perioperative variable costs. *Anesthesiology.* 2002;96:718–724; Silvestry SC, Smith PK. Current status of cardiac surgery in the abciximab-treated patient. *Ann Thorac Surg.* 2000;70:S12–S19.
[§]Variable cost of blood products reflects the incremental hospital cost of a single unit transfusion when compared to similar patients receiving autologous blood or no transfusion, and likely reflect adverse effects and increased resource consumption associated with allogeneic blood.

approach $400 million per year and the cost burden to hospitals of transfusion related adverse effects would exceed $10 billion per year. An accounting for long-term adverse effects that result from immune suppression would add further to individual and societal costs of blood transfusions. Several published studies have noted higher tumor recurrence rates and decreased survival in cancer patients that have received transfusions (19,20, 69,70), and studies have also documented higher short-term and long-term mortality in transfused versus nontransfused critical care and cardiac surgery patients (33,37–40).

BLOOD PRODUCT REIMBURSEMENT

Blood costs are estimated to comprise approximately 1% of all hospital costs in the U.S., with 95% of blood being transfused in the inpatient setting (6,71). While blood and blood related costs are a small percentage of most hospital's budgets, this amount can represent several million dollars a year to a medium-sized hospital, and significantly more for larger hospitals or those delivering blood intensive services, such as trauma, organ transplants, or cancer care. If rising blood costs can simply be passed on to the end consumer (patient, insurer) in the form of higher charges or fees for services, then they pose little threat to the profitability of the hospital. However, this is typically not the case.

Current Reimbursement System

Medicare is the predominant payer for blood and blood related services, with Medicare beneficiaries receiving almost half of all blood transfusions (Fig. 2.16) (6). In 1983, Medicare established the Prospective Payment System (PPS) for hospital inpatient services provided to Medicare beneficiaries. Under this system, a hospital is paid a fixed amount for each patient discharged in a particular treatment category or Diagnosis Related Group (DRG). This fixed amount is intended to cover the cost of treating a typical patient for a particular DRG and encourages hospitals to manage their operations and delivery of care more efficiently. Updates to this PPS are done annually, using

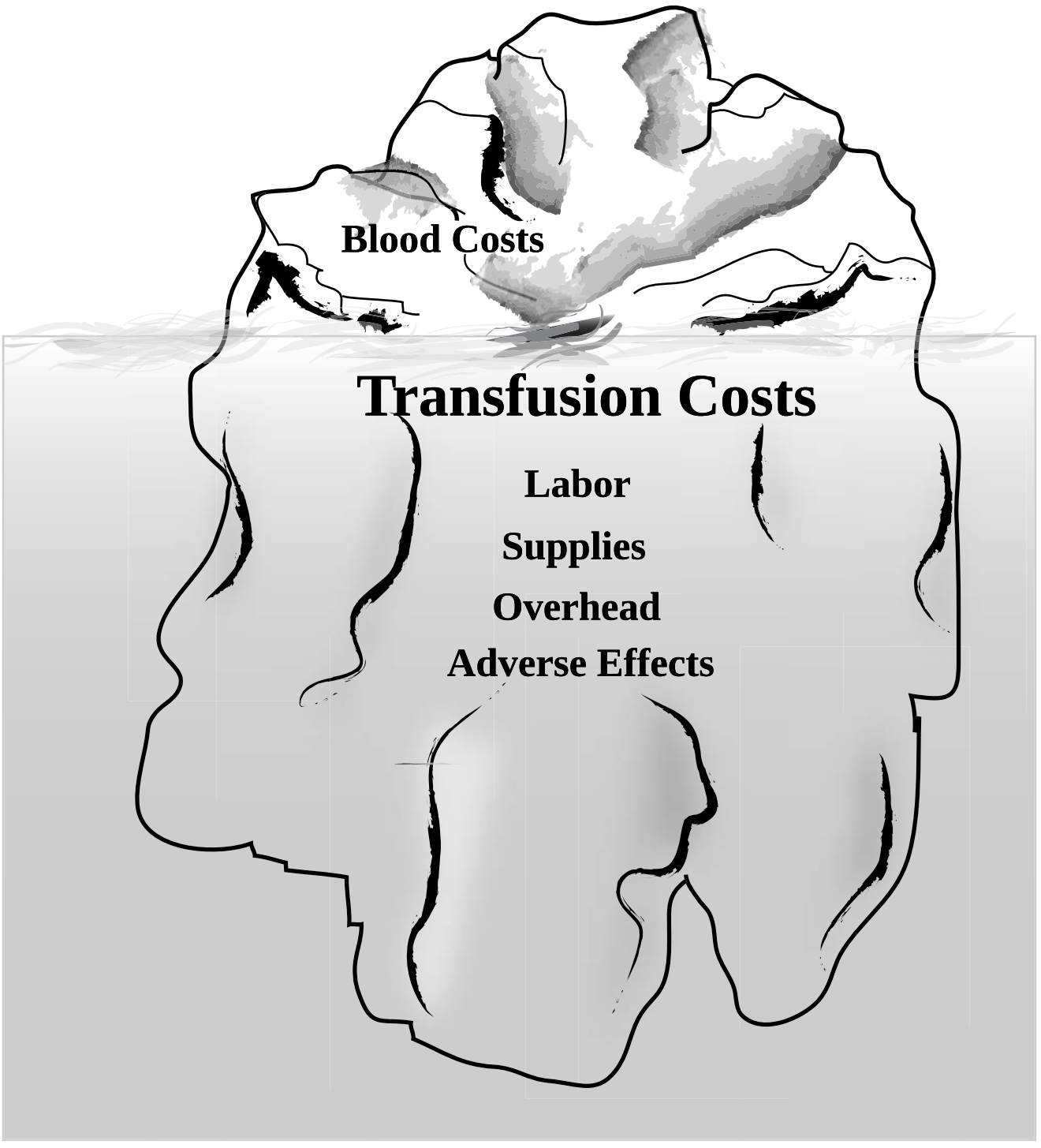


Figure 2.15 The tip of the iceberg. Transfusion costs are substantially more than blood costs, reflecting the consumption of numerous hospital resources as well as the incidence of adverse events associated with blood transfusions.

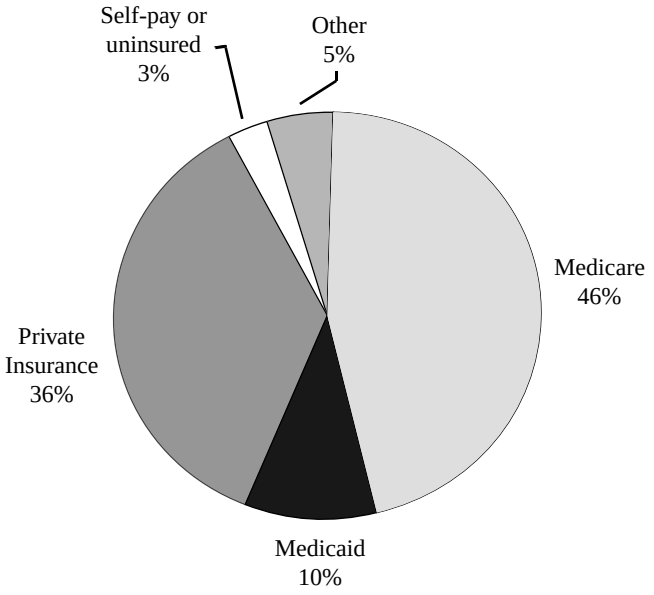


Figure 2.16 Hospital blood transfusions by payer type. Nearly two thirds of all blood products are transfused to Medicare, Medicaid, or uninsured patients. Redrawn with permission from Goodman C, Chan S, Collins P, et al. Ensuring blood safety and availability in the U.S.: technological advances, costs and challenges to payments—final report. *Transfusion.* 2003;43:8 (suppl):31S.

hospital charge data from the previous year and a set of producer price indexes (PPIs) to adjust the price of the market basket for hospital goods and services (6,72). After recalibrating the DRG payments from this information, the Centers for Medicare and Medicaid Services (CMS) publish the new DRG payments for the following year. Inherent to this system is a 2-year lag in payment adjustments after cost increases are actually incurred. Further, the ability of this system to reflect adequate reimbursement rates requires accurate cost and charge information to be submitted by hospitals and that the market basket PPI adequately captures increases in the cost of hospital goods and services. A similar outpatient PPS was instituted by CMS in 2000, using ambulatory payment classifications (APCs).

Private insurance payers and state Medicaid programs also typically use one of several inpatient and outpatient prospective payment systems, rather than reimbursing hospitals for line item charges. Similar to Medicare PPS, these payers use all-inclusive case rates, per diem rates, or rates that use a DRG-like system. Also like Medicare PPS, these systems have inherent problems in accurately capturing and adequately reimbursing hospitals for their actual costs.

Problems with Current Reimbursement System

Following large price increases for blood products beginning in the late 1990s, various groups raised concerns about the Medicare reimbursement system's ability to reflect the cost increases incurred by hospitals. These groups included the American Hospital Association (AHA), the American Association of Blood Banks (AABB), as well as the ARC and ABC. Two large reports have been published reviewing blood cost and reimbursement issues. The first was published as a report to Congress by the Medicare Payment Advisory Committee (MedPAC) in 2001 (72), and the second was a comprehensive document published by the Lewin Group in 2002 (6). The Lewin Group was commissioned by The Advanced Medical Technology Association (AdvaMed), a large trade association which represents manufacturers of medical devices, diagnostic products, and medical information systems. The findings of both of these reports point to systemic problems in capturing, coding, billing, reporting, and reimbursing for blood and blood related costs. Specific findings included:

- The PPI used to represent changes in blood costs was flawed in that it was based on an inappropriate category (industrial chemicals), and PPIs by their nature adjust for inflation but not for technologic advancements or shifts in utilization patterns (6,72).
- There were systematic problems related to undercoding of blood products, meaning failure to code properly, or at all, for blood products, and inaccurate charging, where hospitals fail to charge accurately, or at all, for blood products. The Lewin Group cited a 2002 CMS report showing that only 48.0% of hospitals billed at all for blood products, and, of those that did bill for blood, 90% billed for only one of the two cost centers (6). This indicates that most hospitals either billed for the blood products themselves or for blood related services, but not both. A 1995 survey of blood costs and charges at 60 university hospitals also noted a significant percentage of transfusions did not have associated charges (71).
- Hospital charges are based on markups over hospital costs. Hospital blood related markups varied widely from state to state, but the national average was 73%, meaning that blood charges were at a 27% discount to actual blood costs. This compares to average markups of 182% for medical supplies and 167% for ancillary services (6).

Three major recommendations were made from these reports. CMS was asked to consolidate and clarify its inpatient billing procedures and allowable charges for blood and blood related services, and to incorporate a new PPI specific for blood products. These recommendations are currently under review by CMS. The other recommendation was for blood collection agencies and blood banking organizations to provide ongoing educational and training programs on current coding and billing practices for blood and blood related services. Since 2002, the AABB, ARC, and ABC have all sponsored educational programs on blood coding and billing practices.

ECONOMICS OF BLOOD CONSERVATION

In spite of the doubling of blood acquisition costs in the past few years, the additive costs of regulating and administering transfusions, and the inability to readily pass on these costs, only a small minority of U.S. hospitals currently have active blood conservation programs. At present, there is a general lack of emphasis for blood conservation measures, and misperceptions about the availability and relative costs of suitable methods to reduce allogeneic transfusions.

Alternatives to Transfusions

Transfusion alternatives are therapies that reduce the need for allogeneic transfusions. This would include autotransfusion devices that recycle blood in the operating room or postoperatively, topical hemostatic agents and systemic drugs that reduce bleeding, as well as surgical and anesthetic techniques that minimize perioperative blood loss. The latter category includes careful surgical dissection, minimally invasive surgical approaches, coagulating scalpels, patient temperature maintenance, controlled hypotension, and normovolemic hemodilution techniques (73). Hematopoietic growth factors such as erythropoietin stimulate the production of red blood cells in cancer patients, surgical patients, and critical care patients (74–76). Point of care laboratory tests facilitate efficient transfusion decisions by providing timely information about hemoglobin level and coagulation status (77), and measures to reduce the volume of blood draws in critical care patients can substantially reduce so-called iatrogenic blood loss (78). The most challenging but potentially the most effective method to reduce allogeneic transfusion is to develop systems that promote the use of evidence-based transfusion guidelines (79,80).

Adoption Roadblocks

Despite continued advances in transfusion alternatives, a number of roadblocks exist which reduce the probability of adoption. First, with prospective payment reimbursement, there are no financial incentives or pass-through reimbursement for capital equipment or expensive drugs that can reduce the need for allogeneic blood, nor is there support for administrative overhead involved in administering blood conservation programs. Second, under intense cost pressures, many hospital administrators as well as clinicians make poor economic decisions when comparing the cost of transfusion alternatives to the total costs of transfusing allogeneic blood products. Further, these decision makers can easily become confused when consulting the medical literature that deals with various economic or pseudo-economic analyses of the efficacy of transfusion alternatives. In general, the quality of most studies on the economics of transfusion alternatives is poor. Published papers often conflict on their conclusions about the cost effectiveness of a particular therapy, such as the use of autotransfusion (cell saver) or expensive drugs, such as erythropoietin, aprotinin, and recombinant factor seven (rVIIa). These differing conclusions about similar therapies are often due to differences in the stated objectives, cost methodologies, study perspectives, time periods, and region or country where the analysis was performed. Because of this lack of standardization for study methodology, there is also the potential for significant author bias. It is beyond the scope of this chapter to discuss this literature in detail. However, a discussion of the types of economic analyses and their utility for making local and system decisions provides a foundation for the critical review of published medical economic studies.

Framework for Assessment

While authors often use the term *cost effectiveness* to describe various types of economic analyses, there is a significant difference in the types of studies that seek to evaluate the trade off between costs incurred and benefits gained for a particular therapy. Economic evaluations are divided into types based upon how the outcome of the therapy was measured; specifically, these include cost comparison, cost effectiveness, cost benefit, and cost utility analysis. Table 2.6 summarizes these different measurement schemes as well as the setting in which each is most frequently used.

Cost-comparison analysis is a simple comparison of the direct costs of two competing therapies, and is also known as cost-minimization analysis. While simple to do, this type of analysis is rarely appropriate in the clinical setting because it assumes that all outcomes of the therapies being compared are the same. If, in fact, the outcomes differ, then the total costs of a particular therapy would not be captured. Many published studies use this simplistic and incomplete type of analysis. It is also the most common type of informal analysis done at the departmental level.

The use of a cost-comparison analysis is particularly hazardous when a departmental silo budget exists. A silo budget occurs when cost centers are assigned to functional units within the organization that do not fully control their revenues and costs, yet they are held accountable for a fixed budget. This situation occurs commonly with hospital pharmacies, where annual budgets are often set based upon historical data (i.e., a percentage of last year's budget) rather than a continuous assessment of goals and requirements. If a pharmacy department is asked to increase costs by the use of new drugs that improve patient outcomes, the pharmacy may resist or decline in spite of published evidence

TABLE 2.6
TYPES OF ECONOMIC ANALYSES

Type of Economic Analysis	Costs and Outcomes Measured	Decision Level
Cost comparison	Simple comparison of direct costs of alternate therapies[a]	Departmental
Cost effectiveness	Cost of a treatment to achieve specific outcomes expressed in "natural units" such as units of blood avoided or patient outcome measures	Health care facility, health insurance payer
Cost benefit	Total costs of treatment compared to total cost of outcomes	Health care facility, health insurance payer

[a]Assumes similar outcomes with alternate therapies.

supporting improved patient outcomes. In these cases, the pharmacy department generally does not benefit economically from those outcomes despite improvements in quality of care and decreased total costs incurred by the hospital. Thus, while a cost-comparison analysis may result in the pharmacy minimizing its own departmental costs, this outcome may not be efficient from the hospital's perspective.

Cost-effectiveness analysis measures the cost of a treatment to achieve specific outcomes, which are expressed in natural units, such as units of blood avoided, or patient outcome measures, such as reductions in infection rates or days of hospitalization. As such, this method represents a more sophisticated analysis of total costs versus total benefits. Cost-effectiveness analysis is most appropriately performed at the health care facility level, where more flexible methods of budgeting and accountability are required.

Cost-benefit analysis attempts to account for the total costs of a therapy versus the consequences of the therapy expressed in monetary terms. While it is generally easy to obtain the costs incurred to deliver a therapy, it can be difficult to account for the total cost of the outcome, such as the cost of nontreatment, eventual therapy, support costs, return to employment. At the health care facility level, the primary concern should be total costs incurred during the period of care or hospitalization, making cost-effectiveness and/or cost-benefit analysis the most appropriate types. Health care insurance providers are also concerned about costs incurred from a single health care encounter, but they must also evaluate total benefits of a therapy versus total costs incurred over the period of health insurance coverage, such as readmissions, continued need for medications, and long-term adverse effects. Therefore, cost-benefit analysis best captures the health insurance perspective.

The last type of economic evaluation attempts to capture total costs that include the patient and societal perspective. *Cost-utility analysis* measures outcomes in terms of quality of life, willingness to pay, or patient preference between alternate therapies. Outcomes are measured as values or utilities, such as quality adjusted life years (QALYs), a measure that uses societal ratings of a patient's quality of health and relates it to life span. Because cost-utility analysis attempts to capture the broadest scope of costs and consequences for a given treatment, this type of analysis is most useful for national health policy decision makers.

FUTURE TRENDS IN BLOOD AND TRANSFUSION SAFETY AND THE CONCEPT OF MARGINAL RETURNS

There have been substantial increases in the cost of producing blood products over the past decade, and reimbursement for blood products has not adequately reflected these increased costs. It is also clear that blood costs will continue to escalate in the future. As discussed earlier, one of the factors contributing to higher blood prices is the increase in production costs experienced by blood centers. This trend will likely continue as various industry groups advocate the implementation of additional pathogen detection and reduction technologies to further enhance the safety of the blood supply. These technologies have the potential to reduce the incidence of both viral and bacterial contamination of blood products, but at a substantial cost. Universal pathogen reduction technologies, designed as additives or processes to eliminate viral and bacterial contamination, may add as much as $150 to $200 a unit (6). Also on the horizon are increased costs due to information technology, automated processing systems, and bedside patient identification systems. Current trends could easily lead to a doubling of blood costs within 5 years.

The addition of leukoreduction as a blood quality and safety measure is particularly worthy of discussion in the

context of blood costs. Over the last several years, there has been considerable support for leukoreduction because of multiple clinical benefits that include a reduction in HLA alloimmunization and reduced refractoriness to platelet transfusions, a reduced risk of CMV transmission, and fewer acute transfusion reactions (81). In the U.S., advisory committees to the FDA and the Department of Health and Human Services have recommended universal leukoreduction (ULR) of blood products, which is the current practice in Canada and most western European nations (82). Currently, more than 50% of all blood products in the U.S. are leukoreduced, but universal leukoreduction has not yet been accomplished because of ongoing controversy about the benefits of using leukoreduced blood products for all patients versus the costs of implementing such a program.

While it is clear that some, if not all, patients benefit from leukoreduction and that the process is not harmful, it is also clear that the process adds significantly to the acquisition costs of blood products. At an additional cost of $35 to $45 per unit of blood, universal leukoreduction can increase blood acquisition costs by almost 30%. This can easily add hundreds of thousands of dollars to the annual cost of blood products for an individual hospital and is estimated to increase U.S. blood costs by $500 million per year (81). Advocates of ULR contend that the largest economic benefit of leukoreduction would come from reductions in morbidity and mortality associated with TRIM. A reduction in bacterial infections due to the elimination of allogeneic white blood cells as the putative agent of immunosuppression could substantially reduce total costs associated with transfusions. Blumberg and Heal estimated that leukoreduction of all surgical blood transfusions in the U.S. would substantially reduce the morbidity and mortality associated with postoperative bacterial infections, resulting in a savings of thousands of lives and a total cost savings of $6 to $12 billion per year (41). However, the ability of leukoreduction to reduce or eliminate the adverse effects of transfusion, particularly postoperative bacterial infections, remains controversial. Current evidence supports a significant reduction in acute transfusion reactions with ULR, particularly febrile nonhemolytic reactions (52,55,83,84). Evidence for reductions in mortality and postoperative length of stay have been mixed, with some studies showing reductions in mortality but not length of stay (38,47,55), others showing reductions in length of stay but not mortality (51,53), and still others showing no effect (49,50,52,54). As previously discussed, several studies have come to differing conclusions about the ability of ULR to reduce bacterial infections (32,45–55).

At present, there are no well designed prospective studies that demonstrate cost savings from the universal implementation of leukoreduced blood products. However, there is evidence to support economic benefits of leukoreduction in some patient populations. A review of costs and charges in patients having elective colorectal surgery demonstrated an incremental cost of $4500 (in 1995 dollars) for transfused patients receiving non-leukoreduced versus leukoreduced blood products. The increase in hospital costs was attributed primarily to increases in postoperative infections and length of stay in patients receiving non-leukoreduced transfusions (85). In cancer patients receiving multiple transfusions, the use of leukoreduced blood products reduces platelet refractoriness due to HLA alloimmunization, which can significantly reduce the total cost of treatment (86–88). Although definitive evidence of the economic benefits of ULR remains unproven, an accounting for reductions in the costs associated with acute transfusion reactions, reduced inventory management costs by using only leukoreduced products, avoidance of adverse clinical effects as the result of missed indications for leukoreduced products, and a trend towards a reduction in morbidity and length of stay would likely justify the additional cost per unit in all patients. Future cost effectiveness evaluations of ULR will require controlled, prospective evaluations that carefully account for all adverse effects and total costs in leukoreduced versus non-leukoreduced groups.

Some experts within the transfusion medicine community have advocated a shift in emphasis from further increases in blood safety towards a broader emphasis on transfusion safety (89–91). Blood safety focuses on the safety of the blood component and is the responsibility of regulatory agencies and blood collection centers, while transfusion safety encompasses the overall process that ultimately results in the delivery of safe and appropriate transfusion therapies to patients in hospitals (89) (Fig. 2.17). Transfusion of blood products to the wrong patient (mistransfusion) is currently one of the greatest safety risks of blood transfusions and occurs with the alarming frequency of 1:12,000 to 19,000 units transfused, with death occurring in 1:600,000 to 800,000 transfusions (92,93). Most concerning is that the frequency of mistransfusion has not changed over the past 20 years, while the focus of the blood bank community has remained on incremental reductions in pathogen transmission. Transfusion safety should also include mechanisms to promote optimal blood utilization by reducing inefficiencies associated with inappropriate blood ordering practices. There are several studies that document poor compliance with appropriate transfusion guidelines as well as a tremendous variability in transfusion practice among individual physicians and between different institutions (94–97) (Fig. 2.18). The source of this variation is a lack of formal education in transfusion medicine for nearly all physicians, and varying degrees of awareness and interest among physicians about the current indications for blood transfusions. In total, these

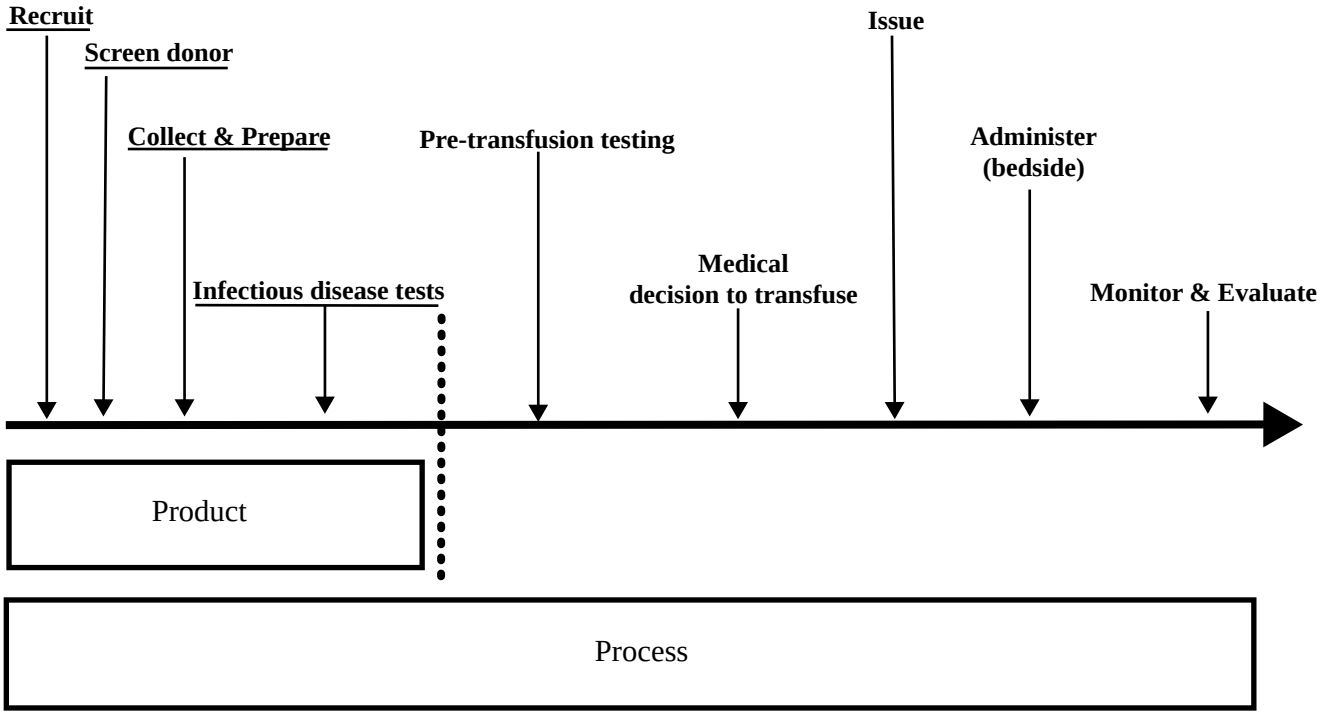


Figure 2.17 Transfusion safety is more than blood product safety and encompasses the overall process from donor collection to recipient transfusion that ultimately results in the delivery of safe and appropriate transfusion therapies. Redrawn with permission from Dzik WH. Emily Cooley Lecture 2002: transfusion safety in hospital. *Transfusion.* 2003;43(9):1191.

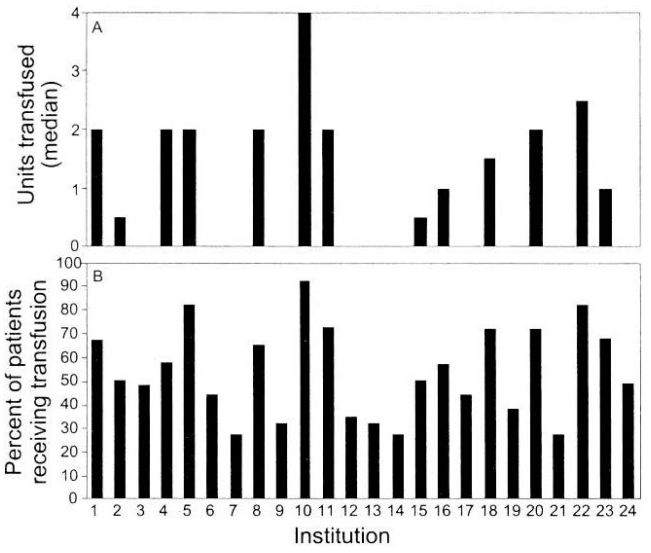


Figure 2.18 Variation in transfusion rates for primary coronary artery bypass surgery at 24 institutions. Red blood cell transfusion rates varied from 27% to 92%, and coagulation factor transfusion rates varied from 0% to 36%. Reprinted with permission from Stover EP, Siegel LC, Parks R, et al. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. *Anesthesiology.* 1998;88(2):327–333.

comments suggest that the marginal benefit associated with each additional dollar spent on blood safety advancements may be declining. From an economic perspective, this phenomenon is referred to as the concept of diminishing marginal return. In other words, given a blood supply that is already extremely safe, any additional marginal reduction in pathogen risk would require a substantial monetary investment. Thus, additional blood product safety efforts may represent an inefficient use of resources that, as a secondary effect, are contributing to rising blood product prices. However, the marginal benefit associated with a given investment in transfusion safety at the hospital level could be significant.

Transfusion safety advocates have called for the use of positive patient identification systems to reduce the possibility of human error in the transfusion process (89,98). While these systems would add to the cost of transfusing blood products, a reduction in errors from mistransfusion has the potential to reduce total costs by preventing serious complications, saving lives and reducing liability for hospitals. Optimal blood utilization is also a key element of transfusion safety, because unnecessary transfusion of blood products is not only inefficient but can cause significant harm to patients (99,100). A continuous review of blood ordering practices and an aggressive educational program about the risks, benefits, and appropriate indications

for blood transfusions are required to promote optimal blood use. Several studies have demonstrated substantial reductions in departmental and total hospital blood use after the implementation of evidence based transfusion guidelines (80,101–103). Although the costs of guideline implementation would need to account for the clinical and administrative time to formulate, promulgate and reinforce such guidelines, successful implementation of transfusion guidelines would clearly be the most cost effective of all blood conservation interventions.

Transfusion safety may be best implemented at the hospital level through the establishment of comprehensive blood management programs. *Blood management* is an evolving concept that integrates quality management, economics, and organizational change theory in order to promote the safe and efficient use of blood resources. Blood management is distinct from the concept of *bloodless medicine*, which is a programmatic approach to dealing with a small subset of patients that refuse blood transfusions because of religious beliefs. Blood management is also a more appropriate term than *blood conservation*, which can imply rationing in response to blood shortages, thereby limiting the scope, acceptance and sustainability of hospital efforts. The goal of blood management is to safely, efficiently, and effectively allocate the scarce resources involved in the complex process of blood utilization. The overriding principles of blood management are:

- utilization of current scientific evidence and the promotion of clinical best practices.
- alignment and coordination of all members of the health care team.
- patient advocacy and patient safety.
- stewardship of scarce and expensive hospital resources.

The cornerstones of blood management programs are the implementation of evidence-based transfusion guidelines to reduce variability in transfusion practice, and the employment of multidisciplinary teams to study, implement, and monitor blood management strategies in clinical areas of high blood consumption.

SUMMARY

Blood is a precious and vital resource that is increasingly scarce and increasingly expensive. A variety of demand-side and supply-side factors have put upward pressure on the price of blood products in recent years. Blood acquisition costs are only a small part of total transfusion costs that hospitals must shoulder, however. In particular, measurement of total transfusion costs requires the inclusion of direct costs (e.g., blood procurement, labor, supplies, overhead), indirect costs (e.g., adverse effects of transfusions), and opportunity costs (e.g., donor direct and indirect costs, blood shortages and surgery cancellations). The increasing cost of transfusions is particularly problematic for hospitals given the current state of the reimbursement system. Constrained by the Medicare Prospective Payment System (PPS), hospitals are limited in their ability to pass increasing blood related costs along to the end consumer in the form of higher fees. Hospitals need to properly code and bill for blood and blood related services, and reimbursement systems must account for the increasing costs of purchasing, storing, administering, and regulating blood products.

Faced with a tenuous blood supply, increasing blood costs, and inadequate reimbursement systems, hospitals should work toward altering blood demand by improving blood utilization and by the selective use of transfusion alternatives. The appropriateness of these transfusion alternatives must be carefully assessed using proper cost-effectiveness and cost-benefit analyses. There is evidence that investments in patient safety systems and mechanisms to promote optimal blood utilization may offer a greater marginal return than similar investments in blood product safety. The establishment of comprehensive blood management programs would lead to more efficient use of blood resources today and could ultimately result in stabilization of blood prices and fewer blood shortages in the future.

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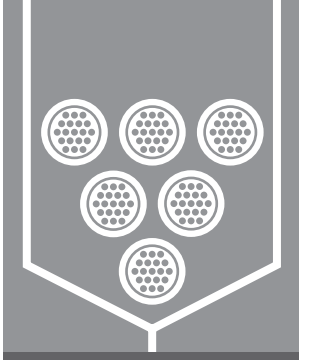

3

Blood Supplies Now and in the Future

Mike Fitzpatrick

Since the 1960s the nation's blood supply has been a subject of government and private studies, discussions, and questions. At that time, the nation's blood supply was collected by the American Red Cross (40%), American Association of Blood Banks (AABB) accredited hospital-based and community-based blood centers (35%; some were paid donors), and commercial blood banks and hospitals (15%). The AABB was formed to establish voluntary standards for donor screening, blood collection and preservation, and testing. The Division of Biologics at the National Institutes of Health was the first federal agency to license blood products and collection establishments. Obtaining and analyzing *national* collection and usage figures has always been difficult because the type and number of blood collection agencies. Most studies have focused on whole blood and red cell collections while the variety of collection methods and components manufactured has grown significantly. The ability to collect in plastic bags resulted in the manufacturing of red blood cells, plasma, and platelets from one unit of whole blood. Automated instruments have improved collection methods adding single donor platelets, jumbo plasma, dual red cell collections, peripheral blood stem cells, and a number of specialty products. There is no central system to monitor the collection or usage of any of these products.

The National Blood Policy, established by the Department of Health Education and Welfare in 1973, called for developing a safe, fast, and efficient blood collection and distribution system. The policy also described specific improvements in blood banking to include: regionalized blood collection and distribution; transition to an all voluntary blood donation system, and rational alignment of charges and costs for blood services. It also stated that if the private sector could not satisfactorily progress toward its implementation a legislative or regulatory approach would have to be considered. Several agencies formed the American Blood Commission to implement the plan, but funding problems and interagency rivalry kept the commission from being successful.

In 1973, in 1999, and again in 2002, the General Accounting Office (GAO) attempted to assess the state of the national blood supply.

In 1999 Congress requested that the GAO review the current status of the ability of the blood supply to meet projected demand. The GAO report, "Blood Supply, Availability of Blood to Meet the Nation's Requirements" responded to a recent report by the National Blood Data Resource Center which projected that the demand for blood will outstrip the available supply by the year 2000. At the same time, the Food and Drug Administration (FDA) recommended prohibiting blood donations from individuals who spent 6 months or more in the United Kingdom between 1980 and the end of 1996 because of concerns over the possible transmissibility of new variant Creutzfeldt-Jakob disease (nvCJD), the human form of "mad cow" disease which exacerbated the projected shortage. The GAO found that, while there is cause for concern about shortages of certain blood types or in certain regions, the blood supply as a whole was not in crisis. The report indicated that the NBDRC study overstated the decline in the blood supply.

The terrorist attacks of September 11, 2001 reminded the nation of the critical importance of a safe and adequate supply of blood for transfusions. Efforts to understand supply and demand trends have coincided with renewed debate about ensuring the safety and availability of blood. The historically sporadic monitoring of the blood supply led to questions about U.S. blood suppliers' ability to

respond to emergencies. The available data indicate that the blood supply has increased in the last 5 years and that its growth has kept pace with the rise in the demand for blood. Blood collections in the first half of 2001 were significantly greater than for the comparable period in 2000. Blood collections increased nearly 40% in the weeks immediately following September 11, but returned to preattack levels, following the pattern of collections after earlier emergencies. Although local and temporary blood shortages occur from time to time, the inventory of blood in America's hospitals was at historically high levels before September 11 and remained adequate through the first five months of 2002.

The AABB through the National Blood Data Resource Center (NBRDC) surveyed hospitals and collection centers from 1987 through 2001 (Fig. 3.1). Funding for the NBRDC was discontinued after the 2001 survey and the Department of Health and Human Services (DHHS) attempted to monitor the blood supply by monitoring the inventories in a sampling of hospitals and collection centers as a sentinel system. The system included 29 hospitals, which provide their daily reports to DHHS. They are located in Boston, New York, Pittsburgh, Washington, D.C., Atlanta, Miami, Tampa/St. Petersburg, Mobile, New Orleans, Dallas, Chicago, Indianapolis, Iowa City, Minneapolis, Bismarck, Denver, Seattle, Los Angeles, and Tucson.

Available data indicate that 2001 collections had risen even before the increase in donations following September 11. For example, the Red Cross reported a 2.2% growth in total collections for the first seven months of 2001 over the same period in 2000. In addition, reflecting the success of a Red Cross campaign to increase donations, the number of units collected at Red Cross blood centers was 8% higher in July and August 2001 than the number collected during the same period in 2000. Similarly, NBDRC reported that the 26 blood suppliers included in its statistically representative national sample increased blood deliveries to transfusion centers by 5% in May, June, and July 2001, compared with that same period in 2000.

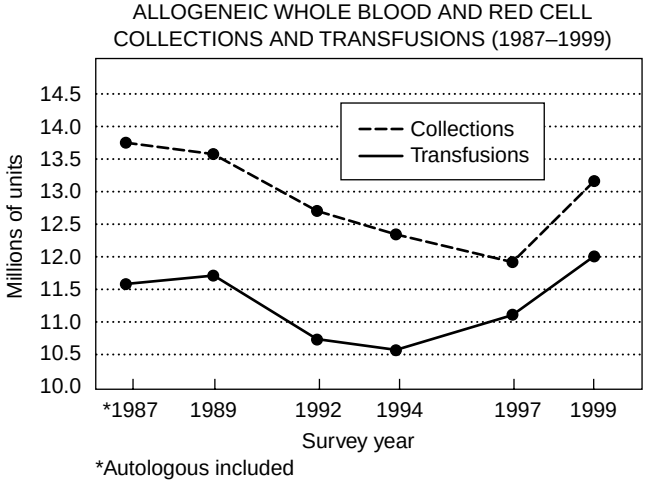

Figure 3.1 Blood collections as compared to transfusion 1987 through 1999. Source: NBDRC.

The high volume of blood donations made immediately after September 11, and the small amount of blood needed to treat survivors, resulted in a national surplus—supply was substantially greater than needed for transfusions. Consequently, the proportion of units that expired and were discarded in October and November 2001 was six times higher than the proportion that expired on an average two-month period in early 2001. Blood suppliers and the federal government are re-evaluating how blood is collected during and after disasters to avert the large amounts of blood that went unused and the logistical strains of collecting unneeded blood. A task force of federal officials and blood supply officials has been created to coordinate blood suppliers' response to future disasters. Incorporating the lessons learned from past disasters, the task force has recommended that blood banks focus on maintaining a consistently adequate nationwide inventory in preparation for disasters and not collecting more blood after a disaster than is medically necessary.

Far more blood was collected immediately after September 11 than was needed by survivors or than ultimately could be absorbed by the nation's blood banks. Estimates of the number of additional units collected nationwide range from 475,000 to 572,000, and fewer than 260 units were used to treat victims of the attacks. Since September 11, federal public health agencies and blood suppliers have found fault with their responses to prior disasters and have begun to plan for a more effective response to future emergencies through an interorganizational task force organized by AABB in late 2001. The focus has shifted away from increasing blood collections in an emergency to maintaining an adequate inventory of blood at all times. This shift was prompted by the realization that a surge in blood collections following a disaster does not help victims because disaster victims rarely require many units of blood and because newly collected blood cannot be used immediately. For example, as with September 11, only a small percentage of the additional blood collected after the Oklahoma City bombing was transfused into victims (131 units of more than 9,000 units collected). Moreover, the units used to treat victims in the hours after a disaster are those already on hand at the treating hospital or local blood bank. It takes 2 days to completely process and test one unit of newly donated blood, so existing stores of blood must be used to treat disaster casualties. Finally, military experts and blood industry officials state that it is unlikely a discrete disaster scenario would require more blood than is normally stored in the nation's blood inventory. They noted that large amounts of blood have neither been needed in building collapses (like the September 11 attacks and the Oklahoma City bombing), nor would blood transfusions be a likely treatment for

illnesses caused by a bioterrorism attack. In fact the most likely scenario to require a large amount of blood is one in which a biological agent is released in a large metropolitan area and all local blood supplies are quarantined and donors are deferred pending the identification of the agent. This scenario would require *immediate* replacement of potentially thousands of units of blood in order maintain care of patients requiring transfusion support. This type of scenario emphasizes the need to have adequate inventories on hand for immediate replacement. The task force has recommended that the national inventory be at a 5-day to 7-day level in order to have adequate replacement stocks available. Platelets are of particular concern in this type of scenario.

CURRENT SUPPLIES

America's Blood Centers (ABC) has the only publicly accessible Web site that provides a daily snapshot of its members' blood supply in the U.S. STOPLIGHT is accessible at http://www.americasblood.org/. This voluntary reporting structure provides a red, yellow, or green indicator of the inventory levels nationally and regionally. Red indicates less than a 1-day supply, yellow a 2-day supply, and green a 3 or more days supply of blood. The 77 U.S. ABC members, who collect about half the blood in the country, report their status daily. The Web site provides a mechanism for comparing the current status of the blood supply to 2 years ago. A recent analysis by ABC reviewed the percentage of the inventory at or above the 3-day level over the past 3 years (Fig. 3.2). Only about 50% of the blood supply is above a 3-day inventory level on any given month. The levels in 2005 are consistently higher than 2004 but are below the April, May, and June levels of 2003. This indicates the continued need to educate the public and increase donation rates so that the inventory levels can be maintained at the 5-day to 7-day level recommended by the task force on a routine basis. The American Red Cross (ARC) has reported a 3% increase in collections over the same time period in 2004.

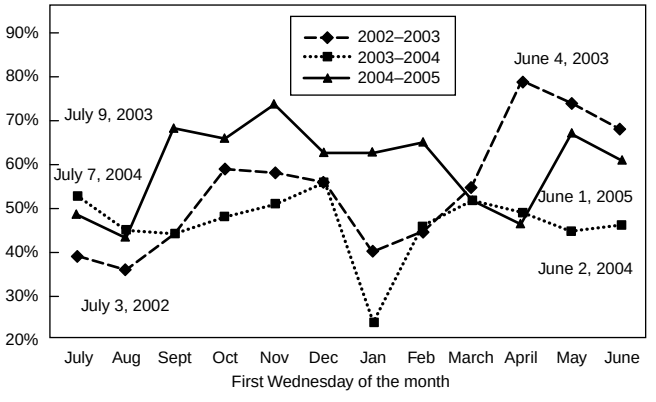

Figure 3.2 STOPLIGHT: percent of America's Blood Centers' blood supply at 3 days or more.

THE FUTURE BLOOD SUPPLY

The Blood Action Plan drafted in 1973 identified blood as a "unique national resource," and blood was identified as a "critical national resource" by Advisory Committee on Blood Safety and Availability in 2001. Yet this country still struggles to increase inventory levels to 3 days or more. The United Kingdom provides public access to their daily inventory levels at http://www.blood.co.uk/pages/stocklevel.html. A review of their historical levels demonstrates that they are able to maintain a 7-day inventory level of O positive red cells. This is an accomplishment beyond comprehension in the United States at this time. The AABB Interorganizational Task Force submitted a plan to the Secretary of Health and Human Services detailing how to increase inventory levels and create a National Blood Reserve. This plan is still valid and is presented here with the permission of the task force.

NATIONAL BLOOD RESERVE

The Need for a National Blood Reserve

Blood is a vital public health resource that must be readily available at all times, especially in the event of a domestic disaster. Therefore, the blood banking community believes it is essential that a national blood reserve be established.

Because the nation's, and particular regions' blood supplies vary throughout the year, there currently is no guarantee that existing supply could meet the emergency needs of victims of a domestic disaster or act of terrorism or of the military. Blood centers strive to maintain sufficient supplies, but with seasonal and regional variations, inventories fluctuate from a 1-day to 4-day supply—significantly below the 7-day inventory recommended by the AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism (Interorganizational Task Force) (1).

Background

The Interorganizational Task Force was formed after September 11, 2001 to ensure the nation's blood needs are met in the event of disaster or act of terrorism. The Interorganizational Task Force currently maintains an information network designed to report as needed to DHHS on the current state of the blood supply with recommendations for action in the event of an emergency. The country is faced with the continuing question of sufficient supply for daily as well as emergency needs. In the

context of emergency needs, the Interorganizational Task Force has recommended that a dual-purpose blood reserve be established to support both civilian and military emergency needs. A recommendation for implementation was presented in January 2004 to the DHHS's Advisory Committee on Blood Safety and Availability. It must be noted that there are still a significant number of issues to be addressed, but the Interorganizational Task Force is prepared to work through those issues and is confident that with appropriate funding the reserve can be established and used as needed.

In determining the need for a special reserve, the task force considered national emergency preparedness exercises such as TopOff 2 and 3 and recent disasters, including September 11, 2001, recent hurricanes, and so forth. These recent incidents have never generated more casualties needing blood than could be handled locally with resupply from surrounding areas. The terrorist bombing of the U. S. embassy in Kenya required substantial blood support because of the hundreds of casualties generated by the collateral damage from the bombing and is the most recent mass casualty incident that required hundreds of units of blood. However, TopOff 2 and 3 (conducted in 2003 and 2005), were national exercises where two major metropolitan areas were struck with biological agents and posed a substantial challenge to the nation's ability locate and transport large inventories of blood quickly. The incidents deferred large numbers of donors essentially shutting off collections in the affected regions and requiring almost immediate resupply because of having to quarantine the current inventories on the shelves. The task force considered these worst case scenarios in order to develop the best way for the country to respond. In general, the most likely scenario in which the blood supply will be affected and a reserve needed is one involving large-scale donor deferrals and/or product quarantine due to exposure to a biological agent.

General Characteristics

Based on this analysis, the Interorganizational Task Force has identified the following general characteristics for a national blood reserve:

- Liquid red blood cells (RBCs)—types A, B, and O
- Approximately 10,000 units
- Designated storage sites
- Available for shipment in 4 to 6 hours
- Rotation of reserve every 2 weeks
- Combination of government and private sector control over 10,000 units

The reserve must consist of actual units that are available and ready for use; in other words, the reserve must be liquid as opposed to frozen. The task force recommends the creation of a liquid reserve, rather than a reserve of frozen blood components. There are significant problems associated with maintaining a frozen reserve. It is difficult to ensure frozen units remain continually in compliance with the frequent changes to Food and Drug Administration (FDA) donor screening requirements (e.g., if, subsequent to freezing a unit, a new question is added to the blood donor questionnaire to screen for an emerging infectious agent, that unit may no longer meet FDA's safety requirements). In order to keep frozen reserves current, stock must be rotated, and buyers for these units must be identified. Additionally, there are several logistical challenges associated with frozen blood, including a slow and costly process for thawing; a limited postthaw shelf-life, and burdensome storage temperature requirements that limit the agility of a frozen reserve program. Lastly, it is costly to freeze and thaw units for a reserve.

The task force recommended that only RBCs be included in the reserve initially. Other components, such as fresh frozen plasma, cryoprecipitate, and plasma for transfusion, may be added to the reserve in the future if it is practical and the need arises. Platelets are not easily included into the program due to their limited 5-day shelf-life, but, if determined to be beneficial, could be added in the future as well.

The task force recommended a reserve of 10,000 units to serve civilian and potential military needs. It was estimated that this is the approximate number of units needed to provide two major metropolitan areas with roughly a 3-day supply (the average amount of time needed to collect, process, and distribute additional supplies to replace lost inventory). The reserve should be held at several designated storage sites, including both DOD sites and regional blood centers (to be designated), across the country. This would ensure that the blood is available anywhere in the country on 4 to 6 hours notice.

The suggested reserve would draw on the strengths of both the private and public sectors. The task force examined a number of programs currently in use by the Department of Defense (DOD) and/or the National Disaster Medical System (NDMS) to assure delivery of pharmaceuticals, medical supplies, or medical care quickly and efficiently in the case of a natural or man-made disaster. Given the need to be addressed, the unique characteristics of blood and the existing collection and distribution system in the United States, the Interorganizational Task Force believes that the country is best served by a *reserve* that invokes a continuum of supply.

These units offer immediate surge capability in any situation ready for rapid response anywhere in the U.S. or the world. DHHS would direct deployment in conjunction with DOD. The additional 8,000 units would be held at selected regional blood centers, providing easy geographic distribution within a 4- to 6-hour response time throughout the country. These units would be under the management of the blood centers, but with actual use in an emergency directed by DHHS based on assessment of the Interorganizational Task Force (using the current model for information

analysis). It is appropriate that regional blood centers, which have established relationships with their donors, control most of the blood in the reserve (Fig. 3.3).

Access to Reserve Supplies

The information exchange occurring within the task force would identify the critical nature of the emergency with respect to the blood supply and recommend action to DHHS. If deemed a disaster, units would be released as necessary from the reserve. Blood centers in the affected area would be allowed to purchase units of blood from the reserve at a significantly reduced rate. The price differential from acquisition to actual sale price to cover an emergency would be the responsibility of the federal government. It should be noted that in order to maintain a cost-effective and manageable reserve, blood in the reserve cannot be accessed to meet local, nondisaster-related shortages. Such local shortages are better addressed through local arrangements as well as a national public and private sector commitment to ensuring a 7-day blood supply nationwide.

Billing and administrative functions associated with these units, especially those units flowing through the DOD centers, could, and would be assigned separately to facilitate billing. These functions could logically be placed with the organization serving as an Executive Agent to the private sector portion of the reserve (as identified in the management structure diagram—see below). These specific functions, as well as several other issues, including transportation contracts, remain to be addressed. Generally speaking, however, the initial costs to establish and maintain the reserve, including the costs associated with rotation are considered start-up and operational costs. That cost is essentially the cost for the right to have an emergency reserve. In the event that the reserve is actually used, the blood center/users would be billed for the cost of the units at a reduced price to be determined. Any differential between the reserve acquisition price and the emergency sales price would be borne by the federal government (see Cost of Reserve below). In addition, the government would be responsible for the cost of transporting such units in emergency circumstances.

Cost of Reserve

Government investment in this, or any, blood reserve is absolutely essential for it to succeed. Current cost estimates to establish the 10,000 unit national blood reserve are approximately $2.6 million in start-up costs and $6.8 million annually to rotate through 10,000 units every 2 weeks.

These estimates include a wide array of costs, including those needed for:

- Construction of sites for the reserve;
- Transportation of blood to and from the reserve;
- Start-up costs for the storage facilities (e.g., new refrigeration equipment);
- Overhead to maintain the reserve (e.g., supplies, power, etc.); and
- Purchase of initial units from blood centers.

The exact cost of the reserve will vary, due to the increased cost of blood stemming from inflation as well as the introduction of new blood safety measures. In addition, the 10% discounted value the task force identified must be tested in real market conditions. As noted, actual expense associated with use of reserve units in a disaster and attributable to the federal government remains to be negotiated, but is anticipated to be the difference between the unit acquisition price (currently estimated at $225 per unit) and the price the blood centers pay to use the units in an emergency. In a worst case scenario for the federal government, the cost would be the number of units actually used in an emergency at a price of $225 per unit. As a final cost consideration, an administrative fee to the Executive Agent must

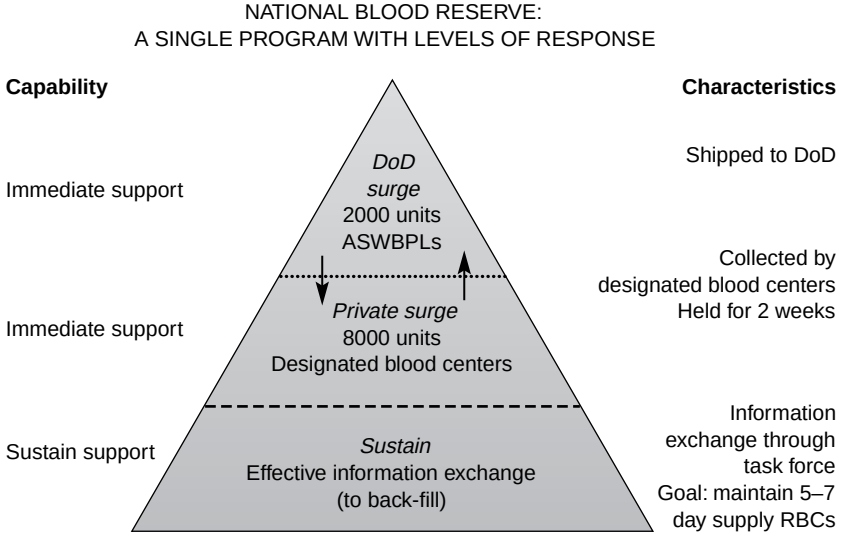

Figure 3.3 Operational characteristics.

be identified and included as part of the operational costs. It is not possible to estimate this fee until all duties to be assigned are identified. AABB would anticipate submitting a cost recovery fee schedule once actual duties are determined.

National Awareness Campaign

The key to success of any blood reserve is a stable and adequate blood supply—that is, a 5-day to 7-day supply. In order to reach this level of inventory, federal support of a national awareness campaign to promote blood donations is essential. The campaign must be focused on the overall need to increase blood donations in every community, rather than donating for the reserve. It should be noted that the Interorganizational Task Force recommends against identifying the locations of individual blood centers holding the reserve in any campaign effort so as not to target them for potential terrorists. Moreover, individuals should not be led to believe that they are donating specifically for a reserve, an issue that has proven problematic in the past. The level of federal investment in this campaign should be at least comparable to DHHS's organ and tissue donation campaigns.

Implementation of Reserve

Several steps must be taken to move the national blood reserve forward and provide the civilian and military populations with a stable, safe blood supply available anywhere in the nation in 4 to 6 hours. These steps include:

- Government approval of the reserve concept and funding of the program.
- Use of existing resources to fill 2,000 unit reserve.
- Government and private sector development of a national awareness campaign.
- Government and private sector development of contracts to fill 8,000 unit reserve. Note: it is critical to select blood centers in the right locations to provide blood within 4 to 6 hours to anywhere in the country.
- Determination of, and agreement with, Executive Agent.
- Task force and government development of policies for authorizing use of the reserve.
- Government and task force establish information processes and tools to manage the reserve.

The nation's blood supply has been a subject of concern for over 50 years. Initial concerns revolved around safety and efficacy of the product. There was general acceptance that shortages would be common because of the short shelf-life and reliance on human volunteers or paid donors for the products. As confidence in the safety of the product has grown, the focus has shifted to availability and disaster response. Each new deferral criteria or infectious disease test removes a percentage of current donors and erodes the supply for a period of time. Historically blood collectors have been able to recruit new donors to replace the deferred ones. The September 11 attacks shifted the focus to response, and even now, almost 5 years later, there is not an adequate supply of blood to meet the demands envisioned by DHHS or the AABB task force. The only way of guaranteeing an adequate blood supply is to harness the energy of the myriad blood collectors and the private and government resources that can make the public aware of the need to donate often. If each donor doubled his or her annual donation rate, the problem would be solved. The blood organizations AABB, ABC, and ARC have taken the first steps by contributing $1.8 million to a public awareness campaign developed with the AdCouncil that will run for 3 years. Only by educating current and future generations of the need to voluntarily donate this precious resource will future supplies be assured.

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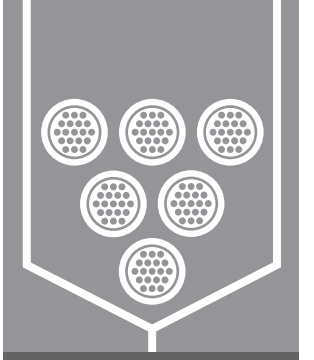

4

Medical Ethics, Transfusion, and the Standard of Practice

Kenneth Kipnis

A PARABLE

We begin with a landmark episode in the history of medicine and the life of the French surgeon, Ambroise Paré (1). It is 1537 and Paré is with the French army at the siege of Turin, treating gunshot wounds by amputating limbs and cauterizing the stumps with heated oil. According to the standard of practice, cautery is needed because gunpowder is poisonous. To his dismay, Paré runs out of oil in the middle of his work and is unable to replenish his supply from other surgeons on the field. In desperation, he treats the remaining patients using egg yolk, oil of roses, and turpentine; he goes to sleep expecting the second group to die during the night. But when he awakes, those treated with the egg mixture have rested and healed well, but those who had been cauterized are in pain with swollen wounds. Contemporary sensibilities will recognize a rudimentary clinical trial and, as Paré did, appreciate the evidence against an established standard of practice.

DEPARTURES FROM THE STANDARD OF PRACTICE

Any statement of a standard of practice in medicine can be put in the following form: Procedure P (which may include a range of options) is medically indicated when conditions A, B, C . . . obtain. The standard of practice may well be the greatest achievement of medicine; the hard-won product of its accumulated knowledge and experience. Nothing in this chapter should detract from its value.

It is broadly accepted that clinicians have to administer blood as a part of treatment for many medical conditions. Since the discovery of blood types, transfusions have significantly improved outcomes for countless patients, and the standard of practice properly reflects an impressive succession of advancements. Even when clinicians do not expect to use blood, they will often want assurance that it is at hand should a need arise. Things being equal, no ethical issues are raised when the standard of practice properly calls for transfusion and a physician acts in accordance with it. (We will set aside the issues that arise when blood is used when the standard of practice does not call for it.)

But things are not always equal. Three distinct situations stimulate debate about the ethics of forgoing the use of blood when the prevailing standard of practice calls for it. In the first type of case, blood is, at the time, a scarce resource. Perhaps, as with Paré, there are many with needs and not enough for everyone. In the second type of case, blood is available but a patient refuses to consent to its use. These refusals are famously common among Jehovah's Witnesses. But as hepatitis, AIDS, Creutzfeldt-Jakob disease, and immune reactions have eroded its reputation, blood is being refused by non-Jehovah's Witnesses as well. The third type of case has to do with medical research which, by its nature, alters the standard of practice. Though transfusions have been critical to the well-being of countless patients, blood has never been an unalloyed blessing. Its risks and limitations are now so well understood that few would mourn the

closing of the last blood bank, provided there were alternatives that were safer and easier to use. Advancements can take the form of instruments, procedures, and drugs that can eliminate, or reduce, the need for blood; and fluids that can somehow serve as safer, more effective, and more easily utilized blood substitutes. But these innovative strategies can come under the standard of practice only after they have been shown in some way to be superior to standard treatment. Accordingly, any research evaluating the performance of promising alternatives to transfusion must involve withholding blood from patients/research subjects who would ordinarily be entitled to it. So—ethically—how can research on alternatives be carried out?

Scarcity, refusals, and research generate the most important ethical problems associated with forgoing the use of blood in clinical medicine. It is the purpose of this chapter to review these three issues and to sketch responsible approaches to each of them. Three critically important concepts will be developed along the way: *disaster triage* in the discussion of scarcity, *decisional capacity* in the context of refusals, and *equipoise* in the context of research.

Scarcity

Medically treatable conditions can be mapped along two dimensions. The first is urgency. Prospective patients can be thought of as arriving with a countdown timer. Though some ailments are self-limiting—patients can be expected to get better on their own—others require timely care. Too much delay and these patients will deteriorate: suffering permanent loss or requiring more care than otherwise would have been needed. This concept—urgency—is intended to capture the idea of a vague time limit. The second dimension is complexity. Every treatable condition will use up resources when treated—time, staff, equipment, clinical space, medical supplies. Taken together, these two factors, urgency and complexity, offer a measurement of the burden of clinical responsibility for a single patient. What do we need to treat the patient (complexity), and how much time do we have to get to it (urgency)? It is an unhappy truth that time and resources are subject to limits. When the burden of responsibility exceeds a clinician's resources, he or she must go to colleagues for help (2).

In a hospital, the stream of prospective patients introduces a third factor: rate. How many prospective patients are presenting per hour? The hospital's burden of clinical responsibility is measured as a function of all three factors—urgency, complexity, and rate. When things go well, a hospital's therapeutic resources (staff, supplies, space) will be at least equal to its clinical responsibility. Clinical triage, commonly done by a nurse, serves to reconcile the flow of prospective patients to the hospital's carrying capacity as these two elements engage each other in the emergency department.

However, when a surge of patients or a staff shortage overwhelms a hospital's carrying capacity, many hospitals use bypass as a first fallback position. They close their doors and divert ambulances to other hospitals nearby. But when a civil disaster occurs, all hospitals in a region can be overloaded and diversion will then fail. What is needed is a second fallback position. Disaster triage is the procedure that comes into play during those critical periods. First developed by the French military, this method of handling large numbers of sick and injured is now a part of every hospital's preparedness (3).

Those presenting for care are characteristically assigned to one of three categories. The sick and injured can be conceived as falling in a bell curve along a horizontal scale, with the most seriously injured toward the right and the walking wounded on the left. Disaster triage reduces a hospital's clinical responsibility by lopping away patients at both ends of the curve: those at the right, who will likely die even if treated, and those at the left, who will likely live even if not treated. Following a disaster, clinicians must firmly narrow their focus solely to the casualties in the middle: those who will live if treated, but die otherwise. Within this group, priority goes to those whose conditions are the most urgent and the least complex. I am told a life-threatening sucking chest wound can be treated by holding a sheet of plastic over the wound.

Unlike everyday clinical care, the mismatch between the hospital's burden of clinical responsibilities and its carrying capacity makes it impossible to prevent every technically avoidable death. The resources are not there. Disaster triage is the solution to a mathematical problem. How should medical work be organized to save the maximum number of lives?

Setting aside their everyday commitment to the needs of the individual patient, doctors attending mass casualties must become stewards of the community's vital medical resources. If there is a prime directive here, it is that nothing can be wasted: not on patients whose needs are not pressing and not on patients who are likely to die despite care.

The obligations of stewardship extend to the blood supply, generating at least three prior ethical responsibilities. First, clinicians have a responsibility to see to the availability of reserves that will be adequate for emergencies. Second, they have a responsibility to have well-founded knowledge of patients' needs for blood: when there is a life-or-death need for it, when the administration of blood can be delayed or omitted, and when transfusion is unlikely to prevent death. And third, if it is possible to treat patients without depleting an inadequate blood supply, clinicians have a duty to understand bloodless and reduced blood techniques and to use them liberally even if the standard of practice requires otherwise. Responsible clinical practice when blood is in short supply and technically avoidable deaths are inevitable cannot be identical with responsible clinical practice when blood is abundant. Accordingly, even if patients

never refused an offer of blood, physicians would still need knowledge and skill of bloodless medicines, at least as long as life-threatening blood shortages are possible.

Refusals

It has not been blood shortages, but refusals to consent to blood that have occasioned the greater anguish. Many clinicians mistakenly liken these refusals to the behavior of noncompliant patients (a term that many ethicists have come to reject) (4). In this category are the diabetics who repeatedly present with ketoacidosis and the smokers and other drug abusers who ignore medical advice to overcome their life-threatening habits. These frequent flyers test doctors' compassion and provoke anger. Physicians may experience them as heretics in the cathedrals of health care, arrogantly defiling the values that have historically informed and ennobled the professional lives of doctors. For example a Jehovah's Witness, who rejects blood in the face of a recommendation, vexes the conscience of the physician. As a matter of medical ethics, how are doctors to think about these skirmishes between the medical profession and a religion whose precepts are often unfamiliar?

INFORMED CONSENT AND DECISIONAL CAPACITATION

For the last 30 years, doctors, philosophers, lawyers, theologians, nurses, hospital administrators, and social workers have sustained a disciplined debate on the ethical dimension of medical practice. We have argued issues at conferences, in an array of professional journals, in the popular media, in the courts, in legislatures, at colleges and universities, and in hospitals. I consider myself privileged to have been a party to that discussion. Although the opinions of American bioethicists are divided on many issues, a broad consensus on the narrow question of when life-sustaining procedures can be withdrawn or withheld, and, more particularly, on the ethical standards that are applicable to refusals of blood by Jehovah's Witnesses has emerged.

I shall, in what follows, try to sketch that consensus. If one had to summarize it in two propositions, the first would be that the ethical standards applicable to adult Jehovah's Witnesses who refuse blood are exactly the same as those applicable to everyone: Jehovah's Witnesses are not a special case. And the second would be that, in general, refusals of blood by adult Jehovah's Witnesses should be respected. The children of Jehovah's Witnesses will also be discussed.

Ethically and legally, informed consent is at the heart of the relationship between health care professionals and patients. In giving it, a patient assumes a measure of responsibility for the decision to implement the medical procedure and—more importantly—gives health care professionals permission to carry it out. A neighbor asks to use your lawnmower, and you say "It's OK to use my lawnmower." Merely by uttering those words, an act that would have been unlawful (taking a lawnmower without permission) becomes unremarkable. To consent is to exercise a remarkable ethical power: "word magic" some might say. Treating patients against their will could be construed as battery, an unauthorized touching. Certainly it would violate medical ethics anywhere in the United States.

If one had to choose a first principle of medical ethics—an axiom from which other standards flowed—it would have to be this: for decisionally capacitated patients (and we will shortly explain that concept), health care professionals must secure informed consent prior to treatment. There is almost no debate about this issue, though there is discussion at the margins, usually cases involving harm to third parties: women in labor who refuse Caesarian sections and TB patients who refuse antibiotic therapy. Even in those cases no consensus contradicts the axiom. Where informed consent has been withheld or withdrawn, health care professionals, lacking the permission they need, are not at liberty to treat.

It follows that relatives and health care professionals have no ethical (or legal) authority to overturn patients' medical decisions against treatment. It further follows that decisionally capacitated Jehovah's Witnesses—like all patients—are entitled to have their refusals of blood respected by their doctors.

The terms *decisionally capacitated* and *decisionally incapacitated* have to be distinguished from the terms *competent* and *incompetent*. The latter term denotes a legal status that is imposed by the courts. A judge, perhaps following the testimony of a psychiatrist, can declare an adult to be legally incompetent and appoint a guardian to make decisions on behalf of the adult, now a ward. (Children are, by default, legally incompetent until they reach majority or are declared emancipated by a judge.)

While judicial declarations of incompetency are rarely medically required, the terms *capacity* and *incapacity* are clinically applicable, action-specific concepts. Although I am technically competent, I lack the capacities to do surgery and fly an airplane. Likewise, in regard to some health care decision, a patient is sufficiently capacitated to make it, if, at a minimum and generally, he or she: (a) understands the problem, (b) understands the available alternatives (including no treatment), and (c) understands the risks and benefits of each of the available alternatives (including no treatment).

Note that what counts as a risk and what counts as a benefit will depend on the patient's values: a facial scar may have one assessment to a fashion model and quite another to a Prussian military officer. Medical paternalism is what we

have come to call the error physicians make when they suppose they can properly and authoritatively impose their own values on patients, making choices for them. Though doctors must comply with patients' refusals of recommended treatment, that obligation does not mean that doctors must comply with patients' demands for treatments they desire.

Finally, the patient must be able to (d) express a choice. Collectively, (a)–(d) describe a set of abilities that amount to the capacity to make a medical treatment decision. It is therefore possible for a legally incompetent patient to be decisionally capacitated—for example, a mature minor—and for a competent patient to be decisionally incapacitated—for example, an otherwise normal patient who is in denial about a medical problem. All adults are presumed to be competent and decisionally capacitated, but the assumption is refutable.

Informed consent is fundamentally a process of patient education and knowledge assessment. The physician speaks with the patient, explaining the patient's underlying condition, what it means to the life of the patient; the options, and the risks and benefits attached to each option (including the option of treatment without blood). A physician allows time for questions and tests the patient's comprehension, going back over what was not understood and then reassessing comprehension. Nothing rules out making a recommendation, with the understanding, of course, that advice need not be taken.

The presence of friends and relatives in the room can be problematic. For, just as Catholics can covertly choose abortions, so Jehovah's Witness should be able to choose transfusions freely without having to sacrifice doctor–patient confidentiality. On the other hand, some Jehovah's Witnesses may want support during the informed consent process: physicians should follow the lead of the patient in determining whether relatives and friends will be present.

It is often argued that a more stringent standard for decisional capacitation should apply when a patient rejects a non-burdensome intervention that promises significant subjective advantages. In these cases, the patient must possess, in addition to (a)–(d) above: (e) some relatively stable set of personal values and (f) the capacity to employ reason in applying these values to the clinical situation. This higher standard is met when the patient can, "tell a story," so to speak, in which the decision, under the circumstances, makes sense against the background of his or her personal values. A simple and highly effective way of determining whether conditions (e) and (f) are met is to ask "Please help me to understand why you are making this decision" and listen carefully for the links that integrate the patient's values, the patient's understanding of the medical problem, and the patient's decision. When confronted with unusual beliefs, it is sometimes helpful to ask those nearest to the patient whether he or she has felt that way for a long time and/or whether the decision and justification make sense to them given what they know about the patient.

In seeking to understand how the patient's decision is supported by the reasoned application of relatively stable values, it is important that health care professionals strive to honor the patient's values even if these are different from their own. Caution should be exercised to ensure that the standard of rationality that is applied to the patient is not outcome-based; i.e., not set so high that only agreement with the physician's advice could count as adequate evidence of decisional capacity. At bottom, the ethical ideal here resonates strongly with Kant's ideal of respect for the dignity of all persons. We are all in the business of trying to create meaningful lives for ourselves and should accord to others the same respect we would demand for ourselves. Within the cathedral of health care, even heretics are entitled to be treated with respect.

DECISIONALLY INCAPACITATED PATIENTS

While decisionally capacitated patients have the ability to accept or refuse recommendations of medical treatment, including blood transfusions, a different approach must be used where patients are decisionally incapacitated. In general, the literature is fairly consistent in recommending a three-step algorithm. First, determine if there is an advance directive. If there is, follow it. Second, if no advance directive is available, apply substituted judgment (see below). And third, if substituted judgment cannot be applied, apply the best interests test. In all of these cases, the ideal is to approximate, as much as possible, the patient's own autonomous decision.

Where an adult patient has lost decisional capacity, medical decisions should be made, ideally, in accordance with some previously executed advance directive. These documents are of two types. Living wills contain instructions for medical treatment in the event the patient becomes incapacitated, while durable powers of attorney delegate the authority to make medical treatment decisions to a proxy who is required to act in accordance with the patient's values. Sometimes the two documents are combined. As an ethical prophylaxis, physicians should urge their patients to prepare such documents when incapacitation is anticipated (elderly people with Alzheimer's disease) or when disagreements are anticipated with or within the patient's family (young men whose families are unaware that they are gay and HIV positive). Families should be informed about these documents before incapacitation occurs. In the U.S., neither relatives nor health care professionals have the legal or ethical power to countermand the provisions in an advance directive. Unambiguous versions of these are commonly available and ought to be respected when incapacitated Jehovah's Witnesses are treated. When a physician has personal reservations about carrying out the provisions

of an advance directive, care should be transferred in a timely way to another doctor who is willing to honor the patient's decision.

In an instance in which a patient who has lost decisional capacity lacks an advance directive, medical decisions should be made in accordance with substituted judgment. In the case of substituted judgment, a physician meets with the patient's friends and family, who are informed about the medical facts: the patient's condition, the options (including no treatment and/or no use of blood), and the advantages and disadvantages of each option. It is an error to ask for their preference or decision. Instead, those who have been close to the patient should be asked about the patient's hopes, beliefs, values, goals, and concerns, as they understood these before incapacitation. The goal is to identify the course of action that the patient would have chosen under the existing circumstances. A possible approach is to begin by saying that the aim is to reach agreement on the best decision rather than who has the right to decide. If all agree on the best course of action, there is no need to designate a decision maker. It is helpful to frame the question so: "What can each of you tell us about the patient that might help us all to decide what decision he or she would make under these circumstances?"

The stories, the quotations, and the recollections will gradually disclose the patient's deepest values and commitments. Only after these matters have been amply explored—with everyone having had a chance to contribute and to hear what others have had to say—should a physician ask "How can we best respect what that this person stands for?" Using this approach, medical decisions will reflect the patient's values, as these are discerned by those who have been closest to the patient and those best situated to be able to report reliably on what those values were. What will generally emerge is a shared acknowledgment of what the patient's decision would have been. In this manner, blood may properly be withheld from a decisionally incapacitated patient, provided the evidence shows that is what the patient would have decided.

Similar conversations are also appropriate even where there is a proxy decision maker designated by a durable power of attorney. Though the designated proxy does have a right to decide, he or she is still required to make that decision in the light of the patient's values. The broad exchange of information can be essential in confirming what those values were.

Finally, when a decisionally incapacitated patient has no advance directive and information is not otherwise available about the patient's values—either the patient has never been capacitated or is a John Doe—medical decisions should be made using the best interests test. For never capacitated patients, it often makes sense to ask "What do we know of this patient's sensitivities (ie., Warmth, comfort, freedom from pain)?" For formerly capacitated patients it can be helpful to ask "What would the reasonable person in the patient's position choose?" While these cases are especially difficult, they do not arise in conjunction with blood-related issues.

Where a treatment modality is not owed to the patient (where consent has been withdrawn or where the procedure is not expected, on balance, to provide a benefit to the patient) this treatment modality may be withdrawn or withheld. The same conditions that justify withholding treatment also justify withdrawing it. There is no presumption that, once begun, no matter how futile, burdensome, or contrary to the patient's wishes, life-sustaining medical procedures must be continued. The maintenance of organic life is not, always and in itself, a benefit to the patient. *Benefit* here is to be understood as relative to the patient's values, as discussed above.

Note that the decision to withdraw or withhold life support is not a decision to abandon the patient. Other treatment modalities, especially pain control and comfort care (aggressive palliative care) may be required.

THE CHILDREN OF JEHOVAH'S WITNESSES

There is now rather useful literature on the topic of medical decision making for minors (5). While there are still many unsettled issues, there are three factors that should carry weight in deciding whether to honor a refusal of medical treatment on behalf of a minor.

The Decisional Capacity of the Minor

The emerging trend, both in law and medical ethics, is to distinguish between mature (i.e., decisionally capacitated) minors and other minors. A minor may have the ability to understand the diagnosis, the treatment options, and the risks and benefits attaching to each, just as an adult. Personal values may be stable and well reflected upon, and not the manifestations of either a developmental phase or a transient or treatable psychiatric condition. There may be grounded confidence that the child will own the decision later on in life. It is now common for medical ethicists to maintain that a refusal to assent to treatment from a mature minor should be given great weight in medical decision making and there are even several court cases in the U.S. that support the right of Jehovah's Witness and other minors to refuse life-prolonging treatment.

The Burdens and Risks of Treatment

Though medical treatments can be risky and burdensome, many doctors tend to focus on the best outcomes and not on the human costs of getting there. Where treatments carry

high personal prices in this way, that factor can call into question whether the treatment is a benefit on balance. The greater the burden and risk, the less clear it is that the physician is doing a favor in treating the child, when the treatment is medically indicated. There are many life-prolonging treatments—chemotherapy for cancer, dialysis for end-stage renal disease, and immuno-suppressive therapies following transplants—that adults commonly reject as too burdensome or too risky to endure. Where Jehovah's Witness parents refuse transfusion for a child, physicians should consider whether the balance between benefit and risk is such that physicians could easily understand it if it had been a non-Jehovah's Witness parent doing the refusing. The fact that Jehovah's Witness parents are withholding consent on religious grounds should carry no weight if the refusal is reasonable. Elective treatments do not become mandatory solely because the decision maker has taken religious values into account.

Further, in considering the burdens to the child, physicians should take into account that state intervention—the imposition of treatment against the expressed wishes of the parents—may itself cause damage to the child and to his or her social support system, and all of this at a time when, because of grave illness, the integrity of the family is likely to be critically important to the child.

The Effectiveness of the Treatment

There is also a need to consider whether the treatment is likely to be effective in securing some significant and subjectively valuable benefit for the child. The strongest case for overriding parental authority will involve treatments that are demonstrably effective—not experimental or investigational—in securing or recovering some significant benefit that is subjectively valuable to the child (e.g., saving the child's life with good function). But where a treatment has less than a 50% chance of realizing such a benefit, and especially where it is burdensome and/or risky, then these two conditions can mean that it is more likely that the child will be harmed by the treatment instead of being helped by it. If, let us say, a certain drug has a side effect that harms everyone who takes it, but provides significant compensating benefits to 30%, then a child has a 70% chance of being harmed by the treatment without any compensating benefit. It would be difficult to argue that parents have an obligation to authorize treatments reasonably expected to harm the child without a compensating benefit and difficult to argue that doctors have a duty to perform procedures that are, on balance, harmful to most of their pediatric patients, even if parents object.

If there are overriding principles here, they are likely these: neither parents nor clinicians may inflict unnecessary pain and suffering on children (abuse) and parents and doctors may not allow the reasonably preventable loss of a child's life or function (neglect).

We speak here as if there were only two choices: ordinary treatment with the use of blood products and ordinary treatment without it, as if the choice for or against blood were the only variable. But there may be other choices. Clinicians can draw on their own and colleagues' knowledge and skill to try to provide the highest quality care without the use of blood. They can assure Jehovah's Witness parents that everything will be done—everything short of accepting the child's death or disability—to respect their request. It is not now known how successful this approach can be, but any progress medicine makes toward the respectful treatment of Jehovah's Witnesses and their children will benefit all patients and not merely those who abstain from blood.

Research

In our discussion of scarcity and refusals, we have examined situations in which physicians may be obliged somehow to practice outside of the standard of practice. They are not at liberty to practice within it. As doctors gain experience with bloodless and reduced blood techniques, trying to adapt themselves to unusual circumstances, it may occur to them—as it did to Paré—that better results might be obtained outside the standard than are possible within it. When historical evidence accrues suggesting safer and more effective alternatives, the time becomes ripe for randomized trials: clinical research that tests proven transfusion techniques head-to-head against promising bloodless and reduced blood alternatives. But, in the absence of scarcity and refusal, is it ethical to withhold proven treatment from randomly selected patients/research subjects, even though the standard of practice unequivocally calls for it? Is it a breach of professional responsibility for a doctor to enroll a patient in such a trial despite a strong hunch that, in the end, the standard treatment will turn out to be better?

The philosopher Benjamin Freedman has mapped what has become the preferred route out of this dilemma. At its heart is the concept of *clinical equipoise*. This condition obtains when "there exists . . . an honest disagreement in the expert clinical community regarding the comparative merits of two or more forms of treatment for a given condition. To be ethical, a controlled clinical trial must begin and be conducted in a continuing state of clinical equipoise—as between the arms of the study—and must, moreover, offer some reasonable hope that the successful conclusion of the

trial will disturb equipoise (that is, resolve the controversy in the expert clinical community)" (6).

Freedman distinguishes between the opinion of the individual physician and the collective judgment of the professional community. It is the profession as a whole—and not the practitioner—that defines the knowledge base of the field and its standard of practice. But when the field itself is divided, with practitioners on both sides and considerations that point in both directions, it becomes possible to randomize consenting patients into the arms of a controlled study without depriving any patient of treatment that is known, by the profession, to be best. Conducted under equipoise, research cannot deprive any patient of what is known to be the best treatment since, given the division in professional judgment, the profession lacks that knowledge. This is a remarkable insight.

In seeking to identify superior treatments, Freedman is mindful that progress can occur on many fronts. In addition to being safer and more effective, treatments can be easier to administer, better tolerated, cheaper, more easily obtained, and less effective but also less toxic in certain ways. There are many factors that can enter into a practitioner's reasonably favoring some treatments over others.

Research may not be merely a good idea. If there is a reasonable difference of opinion within the professional community, then there may be an obligation for the profession to design trials that will disturb equipoise, bringing forth additional knowledge that will resolve the disagreement and definitively improve the practice of medicine. Whenever it is possible to reduce significant uncertainties in the selection of optimal treatment, the deeper social obligations of medicine may require that the profession undertake research that is up to the task.

As the parable of Paré teaches us, medical progress can occur through forced departures from the standard of practice. Without detracting from its centrality to medicine, the standard of practice should never be thought of as a mere sacred talisman, simply protecting those who cleave to it and empowering its devotees. Within any living intellectual tradition, accepted doctrines, no matter how hard-won, must remain in play and subject to revision. Those who dissent can stimulate reflection and progress. They do not deserve derision. Paré should not have had to wait years before publishing his findings. And far from being profound annoyances, scarcity and refusal offer medicine rare opportunities to stretch its capabilities, enlarge its vision, and extend its public worth. Even when forced into radical departures from the standard of practice, clinicians can nonetheless remain impeccably respectful of the deepest sense of professionalism.

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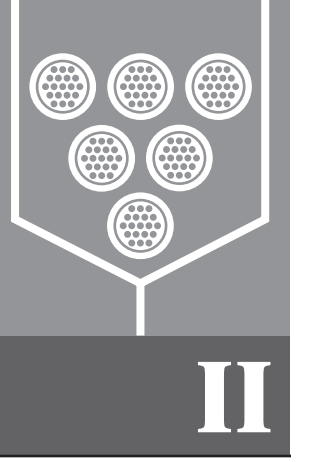
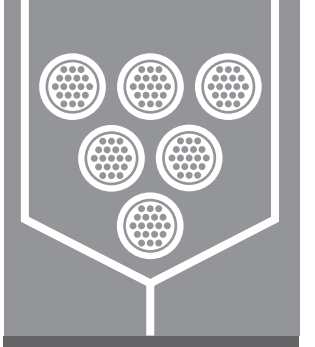


II

The Physiologic Basis for Blood Management: A New Look



5

Oxygen Transport Monitoring: The Basis for Developing Transfusion Triggers

Kevin R. Ward *Ivo Torres Filho*

Donated human blood (packed red blood cells) for transfusion is an extraordinary, valuable, and lifesaving medical resource. Despite this, rigorously tested guidelines and indications for its use are not available. This has led to a staggering level of variance in transfusion practices among and within medical specialties. This is likely the main contributing factor to the almost constant blood shortage in the U.S. leading to regular crisis levels when natural disasters and military conflicts occur. To overcome this, many have advocated the development of transfusion triggers, but just what these should be remain controversial (1–5).

The one and only reason to provide a red blood cell transfusion to a human is to restore or maintain the delivery of oxygen to vital organ systems. Its use for any other reason has no physiologic or medical basis. Although transfusion of blood can be lifesaving, it can also be associated with a number of complications; some of which, such as transmission of infection and allergic reactions, can be understood, but others such as acute organ injury are unexpected and are only now being researched (6).

Everything about the protein hemoglobin and its delivery vehicle (the red blood cell), ranging from the tetrameric structure and cooperativity of hemoglobin to the shape of the red cell, demonstrates its singular purpose in contributing to the transport of oxygen to tissues. Medical science has found it difficult to improve on this design. And the development of hemoglobin-based blood substitutes is likely to have only the advantages of a reduced risk for transmission of infection and fewer restrictions on storage time and conditions making it more available for use in more settings. However, despite the issues above, without a better basic understanding of the indications for use, this newly developed resource will be misused.

THE BASICS OF OXYGEN TRANSPORT

If the sole purpose of transfusion of red blood cells is to restore or maintain oxygen delivery, then the saying "Oxygen is good and blood goes round and round" is the goal. However, just how should clinicians assess and meet this goal? Despite its simplicity, the assessment of tissue oxygenation remains one of the holy grails of medicine. Before discussing this, it is necessary to review some of the basics of oxygen transport.

Oxygen is transported within tissues via microcirculation by convection and diffusion. Convection is the bulk flow of blood and is the process by which substantial amounts of oxygen can be moved rapidly over large distances. Diffusion

Supported in part by grants from the Office of Naval Research
Grants: N00014-02-10344, N00014-03-1-0253, and N00014-02-1-0642
Supported in part by grants from the U.S. Army Medical Research and Materiel Command
Grants: USAMRMC W81K00-04-0998 and DAMD17-03-1-0172

is the random movement of free or bound oxygen molecules and is only efficient at transporting oxygen in the order of tens of microns (7). Almost all oxygen carried by the blood is reversibly bound to hemoglobin within the red cell; this accounts for 98% of oxygen content. Currently there are no clinically proven and available pharmaceuticals capable of enhancing diffusion, so this discussion of oxygen transport will concentrate on convection (7).

Figure 5.1 represents the basic relationship between oxygen consumption (VO_2) and oxygen delivery (DO_2) that is pertinent to individual organs as well as to the whole body. As can be noted, VO_2 can remain constant over a wide range of DO_2. This is because possible tissue beds are capable of efficiently increasing the ratio of extracted oxygen (OER). This will be reflected by decreasing venous hemoglobin oxygen saturation (SvO_2) from each organ. SvO_2 in this setting serves as an indicator of VO_2, mainly as an indicator of the status of DO_2. However, when DO_2 reaches a critical threshold, tissue extraction of oxygen cannot be further increased to meet aerobic tissue demands. It is at this point that VO_2 becomes directly dependent on DO_2 (DO_2crit) and cells begin to convert to anaerobic metabolism as manifested by increases in certain metabolic products such as lactate, NADH, and reduced cytochrome oxidase. The point of DO_2crit is the point of dysoxia, or ischemia, where tissue DO_2 cannot meet tissue oxygen demand (8,9). In addition, DO_2crit can be reached when VO_2 of the tissues has risen above baseline to exceed tissue DO_2, such as may occur during seizures or hyperthermia. DO_2crit will vary among organ systems based on their individual metabolic profiles and their response to neurhumoral factors in acute injury and illness. This is especially true if insults are insidious, allowing for compensation to take place. However, in severe insults such as hemorrhage shock or cardiac arrest, all organ systems will reach a state of DO_2crit nearly simultaneously.

Often overlooked is the fact that there is a carbon dioxide transport mirror of oxygen transport (Fig. 5.2) (10). Because aerobic metabolism generates carbon dioxide and water through its consumption of oxygen, glucose, and other substrates, this is not surprising. For the most part, VO_2 and VCO_2 are tightly coupled and thus parallel each other. The respiratory quotient (RQ) which represents VCO_2/VO_2 is on average 0.85. This is an aggregate measure

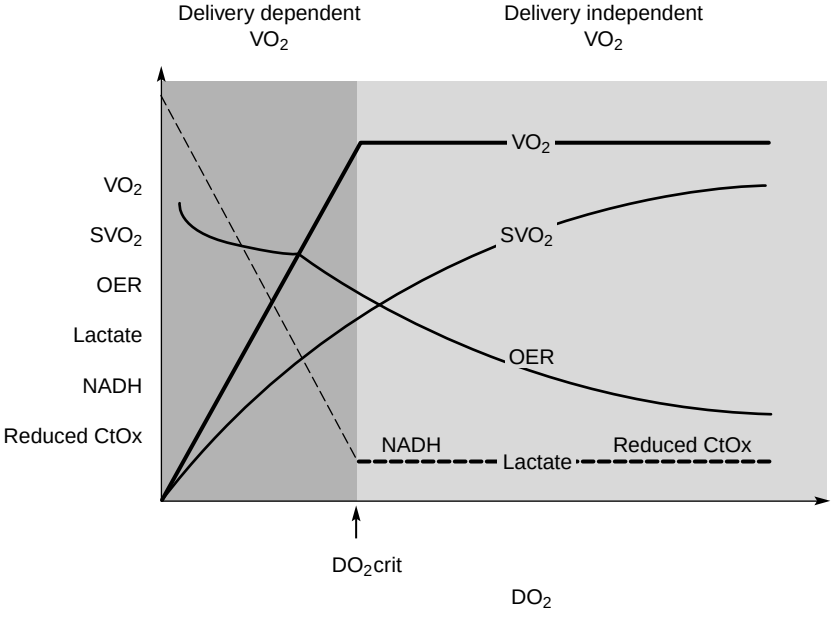


Figure 5.1 Biphasic relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2). Oxygen extraction ratio (OER) increases and mixed venous oxygen saturation (SvO_2) decreases in response to decreased DO_2. Below a critical DO_2 (DO_2crit), VO_2 becomes delivery dependent. DO_2 below DO_2crit results in the beginning of anaerobic metabolism as noted by an increase in a variety of cellular products including lactate, NADH, and reduced cytochrome oxidase (CtOx). The DO_2crit of various organ systems can occur at points either above or below whole body DO_2crit depending on the metabolic and blood flow regulatory characteristics of the organ system and the rapidity of the reductions in DO_2. $DO_2 = CO \times CaO_2$ (normal range: 460 to 650 mL/min/m^2); $VO_2 = CO \times (CaO_2 - CvO_2)$ (normal range: 96 to 170 mL/min/m^2); CaO_2 (arterial oxygen content) = (Hb x 1.39 x SaO_2) + (0.003 x PaO_2); CvO_2 = (Hb x 1.39 x SvO_2) + (0.0003 x PvO_2). CO, Cardiac output; PaO_2, arterial oxygen tension; Hb, hemoglobin, SvO_2 normal range 70% to 80%.

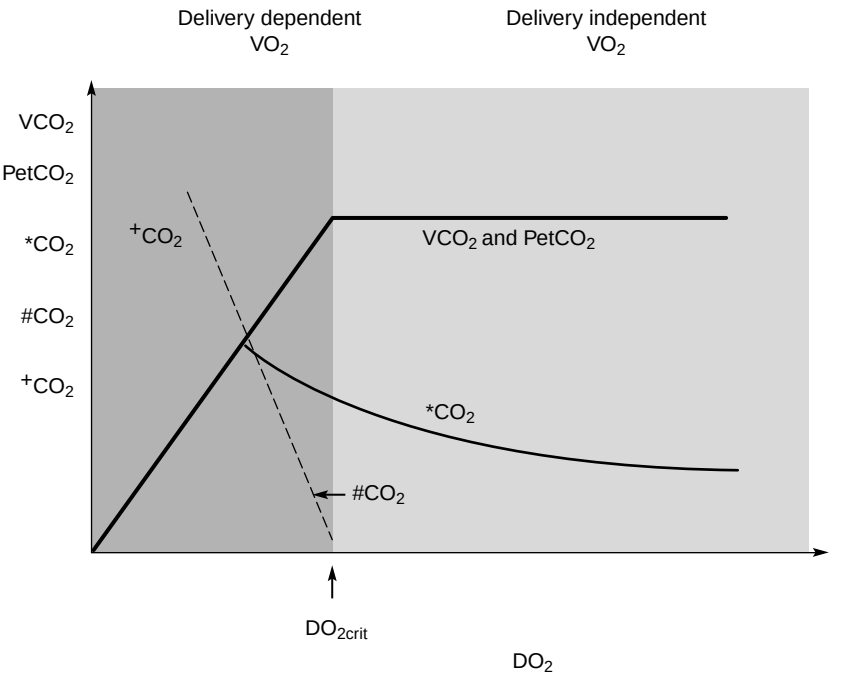


Figure 5.2 Biphasic relationship between DO_2 and VCO_2. Note the similarities between the relationships as compared to Figure 5.1. When minute ventilation is held constant, DO_2crit can be determined by reductions in VCO_2 and thus $PetCO_2$. This corresponds to the point of delivery dependent VO_2. *CO_2 represents CO_2 that accumulates as a result of decreased removal of aerobically produced CO_2 secondary to decreases in flow (respiratory acidosis). #CO_2 represents additional tissue CO_2 production and accumulation due to buffering of metabolic acids produced by anaerobic metabolism after DO_2crit is reached. Overall VCO_2 is decreased due to drops in VO_2. Quantities of CO_2 as depicted on the Y axis are not drawn to scale but instead are depicted to demonstrate their temporal relationship to each other in reference to changes in DO_2.

of the RQ of various organ systems, some of which utilize mainly glucose such as the brain, and others, like the liver, which utilize combinations of substrates such as glucose, protein, and fat. VCO_2 also declines secondary to reductions in actual CO_2 production from decreases in DO_2 (10,11). Although sometimes described as logarithmic, VCO_2 and thus, $PetCO_2$ have almost the same basic biphasic relationship with DO_2 as does VO_2. As such, DO_2crit as been determined by following changes in VCO_2 and thus end-tidal CO_2 ($PetCO_2$) and does not significantly differ compared to determination using changes in VO_2 or lactate production (11–14). Concomitant with reductions in DO_2 will be increases in tissue CO_2 as decreases in blood flow will reduce the amount of aerobically produced CO_2 removed from tissue, creating a tissue respiratory acidosis (12,13,15). Additional tissue CO_2 will be produced after DO_2crit is reached as metabolic acids, such a lactic acid, is buffered by tissue bicarbonate, although tissue CO_2 production as a whole will be decreased in accordance with decreases in VO_2 (15).

The main determinants for whole body DO_2 are cardiac output and oxygen content (16). Therefore reductions in DO_2 may be caused by reductions in cardiac output (heart failure from various causes) or reductions in oxygen content (hemorrhage, profound anemia, hypoxemia). Although this appears simple, it is important to stress at the outset that tissue hemodynamics at the microvascular level are profoundly important, such that while cardiac output from a global DO_2 perspective can be normal or even elevated, tissue DO_2 can be profoundly affected though a number of mechanisms (Fig. 5.3) (17).

Central to the physiology above is the issue of oxygen debt. Oxygen debt can be defined as the amount of cumulative difference of VO_2 between baseline and the amount spent below DO_2crit. The level of accumulated oxygen debt is, to date, the only physiologic variable that is directly linked to survival with, and without, complications of organ failure in the critically ill and injured patient (18–24). Studies in critically ill surgery patients demonstrate little or no mortality when oxygen debt is less than 4,100 mL per m^2. Mortality increases to 50% and 95% when cumulative oxygen debt is 4,900 mL per m^2 and 5,800 mL per m^2, respectively (23,24). This should make sense if oxygen debt is thought of as a quantitative measure of ischemia. The greater the degree of whole body ischemia, the greater the incidence of multiple organ dysfunction, failure, and death. Much of this is linked to the increasing degrees of reperfusion injury and immune dysfunction that occur that are directly correlated with the level of oxygen debt incurred (21,22,25). This is the same paradigm that exists when correlating individual organ ischemia, such as myocardial infarction and stroke, with outcome from these states.

Although less common, problems with VO_2 may be the main determinant of dysoxia such as hyperthermia which might increase VO_2 above available DO_2, or states of cytopathic hypoxia such as cyanide poisoning where cells are unable to use oxygen despite an adequate supply. Cytopathic hypoxia is now believed to exist in states of late sepsis due to mitochondrial dysfunction caused by various inflammatory mediators (26). In this setting DO_2 is above traditional DO_2crit values but tissues remain hypoxic due to this metabolic disorder. Many issues surrounding sepsis

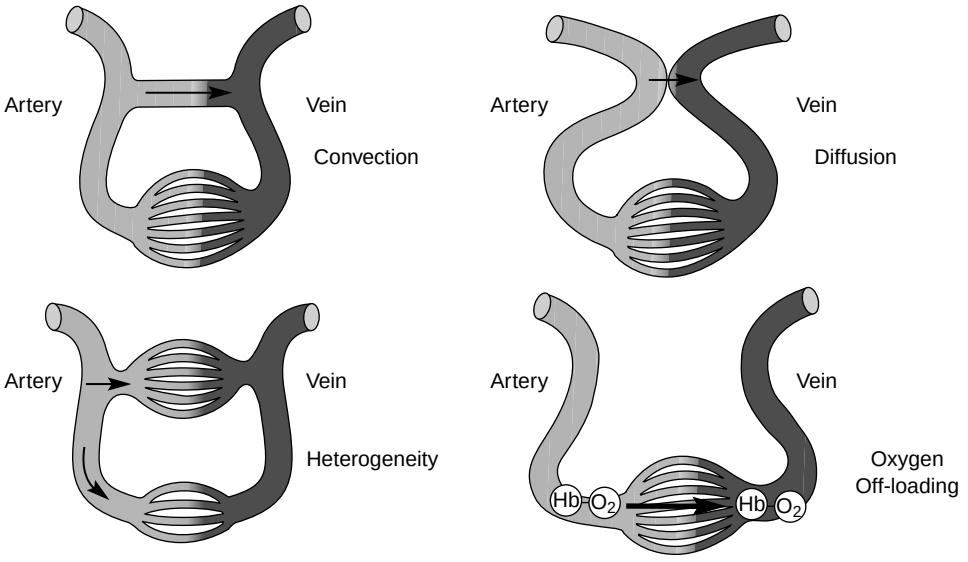


Figure 5.3 Microvascular paradigms, which will alter tissue DO_2 despite no change in global DO_2. Certain mechanisms could result in function shunting thereby actually decreasing oxygen delivery to tissue. Pharmacologic manipulation of the microvasculature may be useful in increasing tissue DO_2 without the need for enhancing CaO_2 through the use of red cell transfusion or the need for enhancing whole body DO_2 through increases in cardiac output. Adapted from Ince C, Sinaasappel M. Microcirculatory oxygenation and shunting in sepsis and shock [see comments]. *Crit Care Med.* 1999;27(7):1369–1377.

and cytopathic hypoxia remain unresolved including its true existence. Despite this, the level of developed oxygen debt will still determine outcome (27).

The means by which red cell transfusion is capable of manipulating the variables associated with oxygen transport are limited but also complex. Clearly, increasing hemoglobin levels will increase oxygen content and in many circumstances, increase cardiac output if cardiac output is reduced secondary to inadequate preload. Bulk convection would appear to be simply and easily increased by increasing circulating hemoglobin levels. However, as is discussed in other chapters in this book, simply increasing oxygen content through raising of hemoglobin levels may not result in the desired effect of increasing tissue oxygen delivery due to problems ranging from the rheologic to biochemical and inflammatory problems caused by use of stored red blood cells which act to potentially reduce oxygen delivery to the tissues (28–32).

Monitoring Oxygen Transport

Based on the previous discussion, what are the best means for clinicians to monitor oxygen transport (oxygen is good, blood goes round and round) of patients and how should information gained by monitoring be used to determine the need for red cell transfusion? In the setting of critical illness and injury, there is now a great deal of discussion regarding monitoring or resuscitation end-points (33). In keeping with the idea that transfusion of red blood cells should serve one purpose (to maintain or restore oxygen delivery to tissues) viewing transfusion as a resuscitative modality is apt. For this reason, transfusion triggers should be viewed in the same way as resuscitation end-points. A good resuscitation end-point would be one that not only detects impending dysoxia and the severity of dysoxia, if present, but also the degree to which the treatment resolves the dysoxia.

Global Oxygen Transport Monitoring

Based on Figure 5.1 it may be tempting to justify direct measures of DO_2 and VO_2, or their components such as cardiac output, to make sure they are within normal ranges; this strategy has categorically failed to change outcome at least in the setting of acute illness and injury (34). Reasons for this are unclear but probably relate to a combination of issues ranging from the physiologic complexity of patients to the time and technical difficulties of preparing patients for measures. In regards to the former, it is likely that the major mistake is settling for DO_2, or component measures (cardiac output or CaO_2), that are in the normal range. The answer to the question "What is the optimal DO_2 for the patient?" should not be a number. It should simply be the DO_2 that results in prevention of, or resolution of, existing dysoxia. Thus monitoring of cardiac output will probably not be helpful except for the extremes of ranges in detecting insufficient cardiac output. In terms of the time and

technical difficulties, use of conventional oxygen transport monitoring tools such as the pulmonary artery catheter make its frequent use cumbersome, time consuming, and dangerous for routine assessment of oxygen transport in determining the need for red cell transfusion. Although noninvasive measures of cardiac output are now available, the same problems will exist in interpreting the values provided as they relate to using cardiac output alone as an end-point for detecting and resolving dysoxia, which can be treated by the transfusion of red blood cells. Use of cardiac output as an end-point unto itself is ill advised since significant end-organ hypoperfusion can exist despite normal and even supernormal cardiac output (35). Instead, a more appropriate use of cardiac output monitoring may be as a guide to volume resuscitation in determining optimal preload (volume challenges provided until no further increase in cardiac output obtained). In addition, its use in conjunction with markers of end-organ perfusion (discussed later) may assist in identifying the points in which pharmacologic therapy to increase cardiac output has been maximized and in turn the need to institute additional circulatory adjuncts such as intra-aortic balloon pumping or use of red cell transfusion is appropriate. The method of cardiac output monitoring used is probably not as important as how and when it is used.

Again, looking at Figures 5.1 and 5.2, it may be tempting to use VO_2 or VCO_2 as a real time guide to the balance of oxygen delivery and consumption. There are several reasons why these are not particularly useful real time measures. These include, but are not limited to, the following: (a) The measure of VO_2 is difficult to make since it relies somewhat on the principle of steady state. VO_2 can be measured using the pulmonary artery catheter and the Fick principle, but this method has been criticized for its potential to be confounded by being mathematically coupled with cardiac output and because it does not account for oxygen consumption by the lungs (16). VO_2 can also be measured using the technique of indirect calorimetry (16). This technique measures oxygen consumption at the airway using devices that measure both airway flow and oxygen content of the flow. Although overcoming problems of mathematic coupling and taking into account oxygen consumption of the lungs, the technique is difficult to use in nonintubated patients and on patients with high inspired concentrations of oxygen. (b) Similar to DO_2 there is a rather wide variation in normal baseline values which will make the acute use of the measure difficult to interpret if one is attempting to ascertain when the patient is experiencing DO_2 dependent VO_2. Changes in core temperature and use of anesthesia can profoundly affect VO_2 without proportional effects on DO_2 (16). Furthermore, because of the biphasic nature of VO_2 and VCO_2, it is difficult to use the measures as early warning that reductions in DO_2 are occurring. However, if minute ventilation is constant, sudden drops of end-tidal PCO_2 (as a reflection of VCO_2 and VO_2) are indicative of passing DO_2crit. VO_2 monitoring can be helpful during resuscitations when trying to ascertain the effects of maneuvers that increase DO_2 or to decrease VO_2. However once a point of DO_2 independent VO_2 is obtained, simply using VO_2 cannot inform the clinician that a state of increased oxygen extraction does not exists.

A valuable surrogate of VO_2 monitoring that may be more helpful in monitoring the state of oxygen transport is mixed venous (SvO_2), or central venous ($ScvO_2$), hemoglobin oxygen saturation monitoring. The use of mixed venous hemoglobin oxygen saturation (SvO_2) has long been advocated as a means to detect tissue hypoxia in critically ill or injured patients since it is a reflection (inversely mirrors) of oxygen extraction which in turn is a reflection of the adequacy of DO_2 (33). Normal values average 75% + 5% making interpretation fairly easy. SvO_2 reflects the aggregate balance between tissue oxygen delivery and consumption or the extraction ratio of all tissues and is thus a reflection of global DO_2 (Fig. 5.1). Since increases in oxygen extraction occur prior to reaching DO_2crit, it is not difficult to understand the potential value of such a measure as an early warning system for identifying significant reductions in DO_2 prior to DO_2crit as well as the need for increasing DO_2 even after reaching a state of VO_2 independent DO_2. Although not truly mixed, a suitable surrogate of SvO_2 may be $ScvO_2$ monitoring. Several studies in trauma and septic patients have demonstrated its usefulness in identifying states tissue hypoxia in the face of normal vital signs and as indicators of the adequacy of resuscitation (36–39). Use of oximetric catheters allow these tools to provide continuous real time data. Certainly patients who have pulmonary artery or central venous catheters in place at the time of transfusion decisions should have SvO_2 or $ScvO_2$ used in their assessment.

Perhaps the current gold standard for detecting whole body dysoxia and the degree of oxygen debt is blood lactate. Lactate is the metabolic product formed in the cytosol of all humans by the process of glycolysis. The amounts formed are normally small because pyruvate, its metabolic precursor, normally enters the mitochondria to be oxidized via the tricarboxylic acid cycle. Therefore, lactate production merely reflects an imbalance between glycolysis and glucose oxidation. The body produces on average 15 to 20 mmole/kg/day of lactate at rest. Lactate consumption occurs primarily in the liver and kidneys but also takes place in the heart, brain, and skeletal muscle. This creates a net normal blood lactate level of 1 to 2 mm.

As noted in Figure 5.1, critical reductions in oxygen delivery (either whole body or regionally) will result in a

state of oxygen delivery dependent oxygen consumption, which will result in a state of significant anaerobic metabolism. This in turn will result in increasing levels of lactate indicative of the degree of oxygen debt. What should not be lost on the clinician is that even relatively small increases in lactate should raise alarms since for elevated levels to develop, lactate must be made, transported out of cells, and then exceed the rate of lactate consumption (mostly by the liver and kidneys). Thus elevated lactate levels can be viewed as a late biochemical finding of altered oxygen transport and should, therefore prompt immediate action. Lactate levels have been demonstrated to be directly proportional to the degree of oxygen debt and lactate has been demonstrated in trauma, sepsis, and heart failure to be more predictive of disease severity and outcome than physical exam (20,21,27,37–40). The degree to which lactate is cleared during treatment is also highly predictive of outcome (37,40). In terms of using lactate as a measure of oxygen debt, interval testing for lactate is more helpful than single levels (27). Thus a patient with a lactate of 3 mM for 8 hours will have incurred more oxygen debt than a patient with a lactate level of 10 mM for 1 hour.

Unless liver failure is present and preventing normal metabolism of lactate, it should be assumed first that elevated lactate levels are due to inadequate tissue oxygen delivery. Clinicians should then rapidly determine which components of oxygen transport should be manipulated to improve oxygen transport and limit oxygen debt. Most important, repetitive lactate testing should take place to determine if improvements in tissue oxygen delivery are taking place.

We have examined many additional diverse biochemical and physiologic parameters that might be potentially used to determine DO_2crit, especially if monitored from a known baseline state (14). The experimental model used was one of isovolemic hemodilution and parameters range from seemingly DO_2 independent signals such as systemic glucose and potassium levels to loosely DO_2 associated signals such as blood pressure and pulse pressure. The data indicate that monitoring a diverse set of easily obtained physiologic and/or biochemical parameters might assist clinicians in determining the need to augment DO_2, especially if monitored from a known baseline.

TISSUE-SPECIFIC MONITORING

In the not too distant past, tissue-specific monitoring was limited to patient symptomatology. This certainly still has an important role, especially in conscious patients with severe coronary artery and/or cerebral vascular disease. Anemic patients complaining of chest pain consistent with myocardial ischemia (especially with corresponding ECG changes) or patients with central nervous system symptoms attributable to decreases in systemic oxygen content should be considered candidates, despite any technologic global or tissue oxygenation technology. The main reason for this is, that despite what might be adequate global DO_2, arterial lesions are acutely compromising tissue flow to the vital organ. In the face of anemia (especially with cardiovascular disease), increasing oxygen content by red cell transfusion is a low energy way of helping to avert local organ damage. For conscious patients with severe anemia, performance of provocative testing, such as undergoing postural changes, might be helpful in looking at the central nervous system's need for increases in oxygen content. Patients who become presyncopal may require transfusion. Examination of any variable that falls within normal limits while patients are at rest may be quite different during activity. However, for many patients for whom transfusion is being entertained, neither the patient's condition nor environment may be conducive to such testing. Thus it will be necessary to perform some assessment of the patient's actual need for transfusion. What then are possible tissue-specific targets?

Again, as noted in Figures 5.1 and 5.2, a biphasic relationship exists between DO_2 and VO_2 or VCO_2, at both the whole body and individual organ or tissue level. The point of DO_2crit varies among organ systems and occurs before whole body DO_2crit is reached in several organ systems (13,33,41). This will be based on their function, metabolic requirements, and response of organs to circulating tissue mediators and to the insult or disease itself that would require transfusion. Studies have demonstrated, for example, that during hemorrhage, the DO_2crit of the splanchnic bed occurs at a higher global DO_2 than the DO_2crit of the whole body (13). However, in massive hemorrhage or other states such as cardiac arrest that lead to sudden and profound reductions in DO_2, the DO_2crit of all organs and thus the whole body will be reached almost simultaneously, whereas slow gastrointestinal bleeding or postoperative anemia may result in certain organ systems reaching DO_2crit earlier than whole body DO_2crit.

The appearance of elevated systemic blood lactate can be interpreted in most instances that DO_2crit of one or more organ systems, if not the whole body, has been reached and thus has limitations in serving as an early warning marker of occult dysoxia except when traditionally compared with vital signs. Overcoming this with real time surrogate measures of OER such as $ScvO_2$ monitoring is desirable but again represents technical challenges in implementation for the majority of patients considered for red cell transfusion. A growing number of technologies

that might be capable of replacing centrally measured $ScvO_2$ and other central measures of gas transport are now becoming available. In addition, these measures are likely to be more sensitive. The technologies are based on several factors of which one or more are shared among them. These major factors are based on the distribution of blood and gas levels among the various vascular compartments and that several tissue sites seem to be metabolically sensitive to reductions in DO_2.

Figure 5.4 demonstrates the distribution of blood and tissue gas levels at the arterial, tissue venous (end-organ), and mixed venous levels during a number of disease processes. As can be noted, arterial values can be normal or elevated while venous (tissue and central) are abnormal. It can be seen from this figure, that if one could have access to the venous effluent from a sensitive organ system, then the adequacy of DO_2 to that tissue could be assessed by examination of either the PO_2, PCO_2, or the SO_2 of the blood. This, of course is not possible. However, because the composition of blood in any volume of tissue is distributed as 70% venous, 20% capillary, and 10% arteriole, methods that can assess aggregate tissue gas parameters will reflect mostly the venous compartment of the tissue, thus possibly substituting as a venous sample from that tissue (42,43). Following are several technologies that are being actively used.

Tissue Oxygen Monitoring

Several options exist to monitor tissue oxygenation, which provides information regarding the balance between DO_2 and VO_2 of the tissue. These include transcutaneous PO_2 ($PtcO_2$) monitoring from the skin, interstitial PO_2 monitoring from tissue parenchyma, and tissue hemoglobin oxygen saturation (StO_2) using spectrophtometric

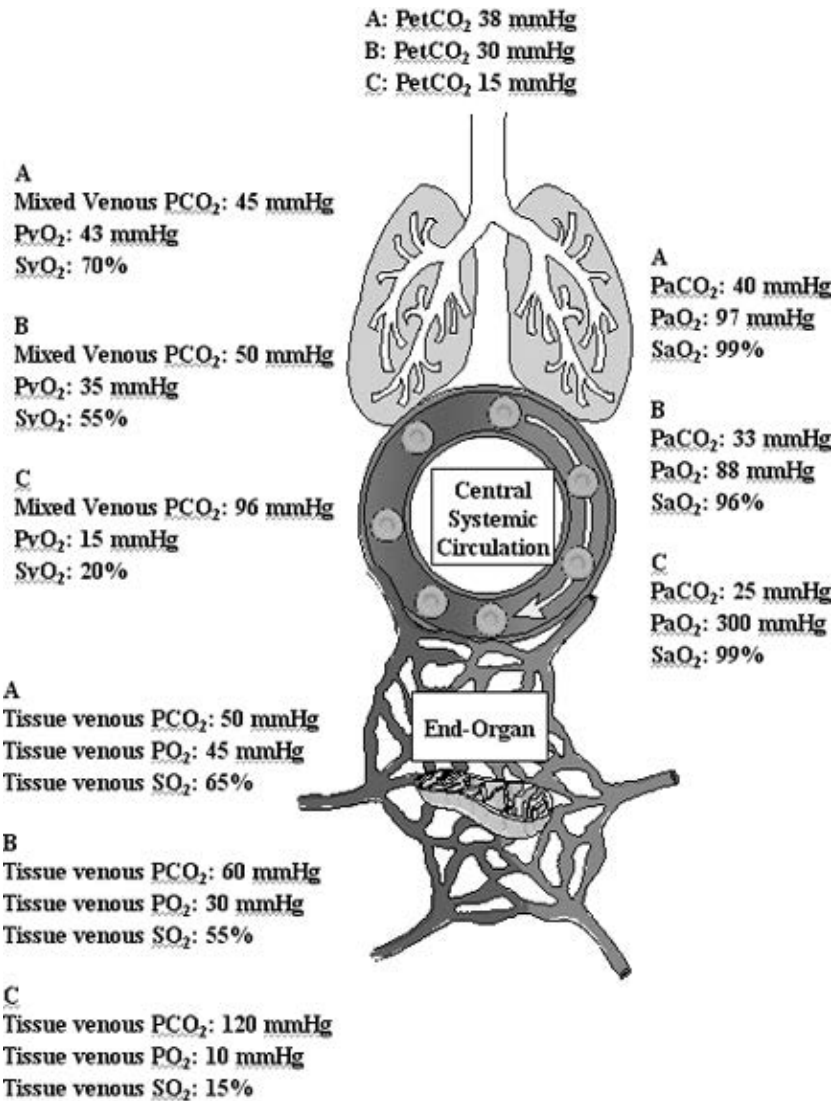


Figure 5.4 Representative blood and tissue gas levels of the (A) normal circulation, (B) moderate hemorrhage or acute anemia, and (C) cardiac arrest. Mixed venous values represent aggregate values from all organ systems. Thus, tissue venous values are not necessarily identical to mixed venous values but can be higher or lower depending on the individual organ system's level of metabolic activity. The majority of blood volume at the level of the tissue is contained in the venous compartment. Cardiac arrest represents the extremes of shock in terms of reduction in DO_2. However, increasing CaO_2 will not help.

techniques such as near infrared absorption spectroscopy (NIRS) (33).

Of special interest is the use of StO_2 monitoring using NIRS. Visible light (450 to 700 nM) penetrates tissue only short distances because it is usually strongly attenuated by various tissue components which absorb and scatter at these wavelengths. In the NIR spectrum (700 to 1100 nM), however, photons are capable of deeper penetration (several centimeters or more) even through bone (44). It is also within this spectral region that oxygen dependent electronic transitions of the metalloproteins hemoglobin and cytochrome oxidase (the terminal electron acceptor in the mitochondrial electron transport chain) absorb light. These chromophores absorb NIR radiation differentially based on their concentration and interaction with oxygen. These changes in absorption can be measured using NIRS technology. The Beer-Lambert law provides the physical and mathematical basis for NIRS although it is modified to account for the inhomogeneous media that the NIR light traverses (44,45). The depth of penetration and volume of tissue begin interrogated by NIRS is dependent on the distance between optodes. The technique of NIRS differs from that of pulse oximetry because pulse oximetry targets only the arterial component of blood flow.

The basis for using NIRS and other spectrophotometric technique to monitor the state of tissue oxygenation relies on the aforementioned compartmentalization of blood volume which in most organ systems is believed to be about 70% venous (42,43). Thus the values obtained by NIRS closely parallel those of venous hemoglobin leaving the tissue. This essentially allows it to be used in the same manner as SvO_2 and $ScvO_2$ except that instead of representing an aggregate reflection of the balance between DO_2 and VO_2 for the entire body, it becomes the reflection of such in an individual organ (skeletal muscle, brain). In addition to being noninvasive, the use of StO_2 monitoring may prove more sensitive over $ScvO_2$ or SvO_2 if the organ being interrogated is sensitive to changes in DO_2 in the setting being monitored. Skeletal muscle and the gastrointestinal tract are two sites explored with NIRS and both appear to be sensitive to decreases in tissue oxygen delivery (46,47).

The vast majority of NIRS technology has been used to monitor the oxygenation status of the brain in neonates and in adults undergoing operative procedures, which may affect the brain such as carotid endarterectomy, or cardiopulmonary bypass. It is also being aggressively studied in the setting of trauma by using skeletal muscle or GI tract as the end-organ of interest (46,47). The NIRS spectra between hemoglobin and myoglobin cannot be distinguished from each other. This is important since myoglobin exists in almost equal proportions to hemoglobin in skeletal muscle with the p50 for myoglobin being only 5 mmHg (48). There is some evidence that when used as an indicator of skeletal muscle oxygenation, the NIRS signal is derived mainly from myoglobin and not hemoglobin within the tissue (49).

Although the potential exists to use NIRS to determine the redox status of the cytochrome oxidase and thus the point of DO_2crit for the organ being monitored, this has proven to be extraordinarily challenging in part because the reduced form of cytochrome oxidase does not have an absorption spectrum and because the amount of cytochrome oxidase is so much smaller compared to hemoglobin (50). In order to use NIRS to monitor the redox state of the mitochondria, monitoring must take place prior to changes in the redox state. This obviously limits the value for monitoring unless performed continuously from a known baseline state.

Tissue Carbon Dioxide Monitoring

Several monitoring options are available to monitor tissue CO_2 and have been studied in various states of critical illness and injury. These include transcutaneous CO_2 ($PtcCO_2$) skin monitoring, interstitial fiberoptic PCO_2, gastric mucosal CO_2 via gastric tonometry ($PgCO_2$), and most recently sublingual tonometry ($PslCO_2$) (33,35,51–58). $PtcCO_2$, $PgCO_2$, and $PslCO_2$ are noninvasive while interstitial PCO_2 monitoring requires probe insertion into tissue parenchyma. The details regarding how CO_2 is actually measured by these techniques has been well described (33). All of these methods are based on the diffusion of CO_2 from tissue. Each of these techniques will reflect the balance between supply of CO_2 to the tissue, CO_2 production by the tissue, and CO_2 removal of the tissue. This balance does not mean all tissue compartments contribute equally. Values will be a composite of vascular and interstitial levels in the immediate environment of the sensor. Since the majority of blood volume in tissues in venous (approximately 70%), the tissue CO_2 concentrations will mainly reflect venous PCO_2 concentrations (42,43). The majority of CO_2 accumulation in each tissue will be secondary to the inability to remove aerobically produced CO_2 that was being produced prior to the actual onset of tissue dysoxia or ischemia (Fig. 5.2). As previously mentioned, additional CO_2 will be produced in response to metabolic acids (mainly lactate) produced after the onset of ischemia by the cells as they are buffered by endogenous bicarbonate stores. Animal and human studies have demonstrated tissue CO_2 levels well over 100 mmHg. Widening of mixed venous to arterial PCO_2 gradient has been known for some time to reflect changes in tissue DO_2 (59,60). However access to the mixed venous pool is not always practical and in fact may not be as sensitive as properly selected peripheral tissue beds.

All of the above methods of tissue PCO_2 monitoring have been demonstrated to be sensitive to microcirculatory

changes in blood flow not reflected in global oxygen transport values such as DO_2 and VO_2. However, since the goal of these measurements is to detect changes in tissue CO_2 as a reflection of changes in DO_2, care must be taken to avoid misinterpretation of the values due to the affects of minute ventilation on tissue PCO_2 which can be significant (56). Since normocapnia cannot always be ensured, use of the tissue CO_2 to $PaCO_2$ gap has been shown to be more sensitive DO_2 related changes in tissue CO_2 since hypoventilation or hyperventilation while affecting tissue CO_2 will not affect the gap. Given the arterial to alveolar PCO_2 gap is approximately 4 mm Hg, it is felt that a tissue to $PetCO_2$ gap of 11 to 14 mm Hg is abnormal and reflective of perfusion abnormalities (53,61). Continued elevation of tissue CO_2 resulting from decreases in tissue DO_2 as measured by these methods has been associated with an increased mortality (51,52,54,62–64). Normalization of the tissue CO_2 to $PetCO_2$ gap will help ensure that occult tissue hypoxia is not present, thus helping to avoid further accumulation of oxygen debt and its associated complications. The major problem with using this strategy may be in patients who have rapidly evolving acute lung injury or who are experiencing significant bronchospasm.

INTRAVITAL MICROSCOPY

The ability to directly and noninvasively visualize microcirculatory blood flow has recently been reduced to clinical practice through the technique of orthogonal polarization spectral imaging (OPSI) (65). Linearly polarized light is used to illuminate the tissue. Because of the wavelength used, the light is reflected by the background and is absorbed by hemoglobin (65–67). Optical filtration allows the elimination of the light reflected at the surface of the tissue to produce high contrast reflected light images of the microcirculation. Red cells appear dark (due to absorption of light by hemoglobin). Vessels, however, are not visible unless they contain red cells. The technique works best on mucosal surfaces. With experience, semiquantitative information regarding microcirculatory hemodynamics is possible by assessing the density of functional (perfused) vessels within the field of view as well as the flow of red cells. Unfortunately, automated software is not yet available for real time quantitative analysis. OPSI of the sublingual area has been used in the evaluation of the microcirculation in patients with sepsis, cardiogenic shock, and during transfusions (66,68,69). The technique provides evidence that the sublingual mucosal surface is sensitive to changes in blood flow and that these changes are reflective of what may be occurring at a more global level. Manipulation of hemodynamic variables has been demonstrated to improve microcirculatory flow. These have included both transfusion as well as vasodilation indicating that rapid feedback can be obtained at a local tissue level in response to acute interventions (70,71). Figure 5.5 demonstrates a patient undergoing cardiopulmonary bypass for coronary artery bypass grafting

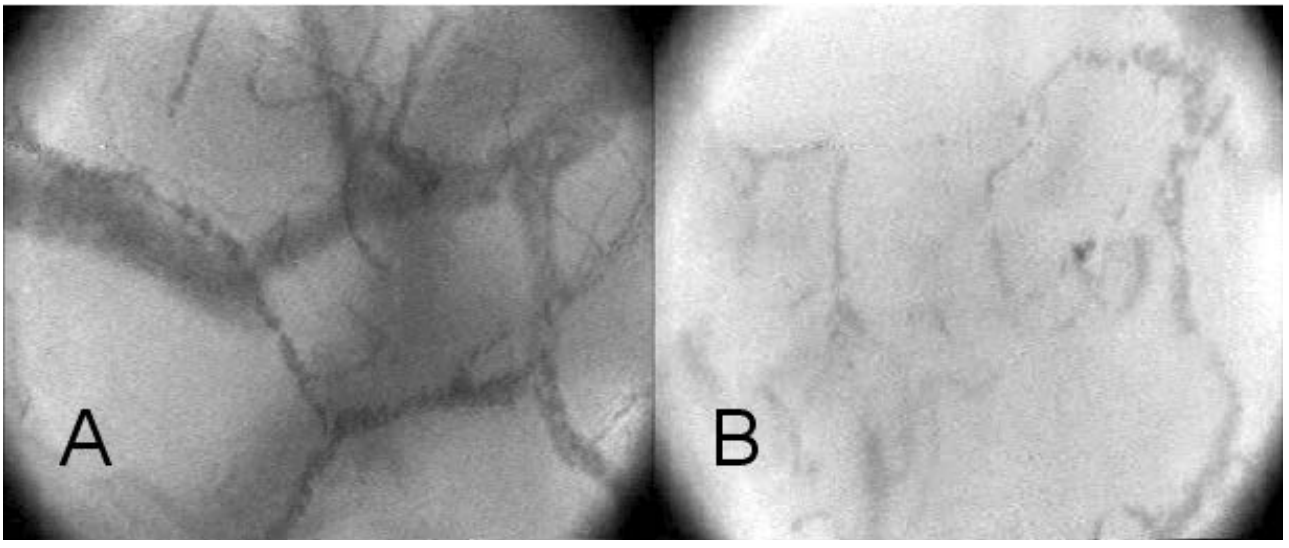


Figure 5.5 Orthogonal polarization spectral imaging of a patient undergoing cardiopulmonary bypass for coronary artery bypass grafting (early in the case (A) and midpoint (B)). Despite no change in vital signs or pump flow, the patient demonstrates a distressed microcirculation as evidenced by a significant reduction in the number of perfused capillaries (B). A lactate level was obtained and was found to be 5 mEq/L as opposed to 1.8 mEq/L in the beginning.

(early in the case and midpoint). Despite no change in vital signs or pump flow, the patient demonstrates a distressed microcirculation as evidenced by a significant reduction in the number of perfused capillaries. A lactate level was obtained and was found to be 5 mEq per L, as opposed to 1.8 meq per L at the outset. The clinician may now use several options to remedy the present state of tissue dysoxia which may or may not include transfusion.

PUTTING IT ALL TOGETHER

The technologies and methods discussed in this chapter are capable of providing the clinician with a more accurate and precise view of tissue oxygenation. However, several important issues require that the technology be balanced with the art of medicine to ensure proper application. These include the following:

1. Patient condition and clinical scenarios are important. Obviously the range of patient conditions and settings are enormous and therefore good judgment is required. The patients who is exsanguinating from a ruptured abdominal aortic aneurysm, lacerated liver, or massive gastrointestinal bleeding does not need high tech monitoring to indicate or justify the provision of red blood cell transfusion. However, monitoring will likely assist in determining when red cell transfusions can be reduced especially as hemorrhage or other factors are controlled. This may help in determining that the stabilizing patient may be adequately oxygenated from a CaO_2 standpoint at a hemoglobin level of 7 gm per dL versus 9 gm per dL. The same provision would exist for the symptomatic anemic patient experiencing myocardial or cerebral ischemia or patients unable to tolerate simple physical activities that might be due to anemia. Resolution of symptoms in these cases are necessary end-points.
2. Patients who are anemic and past their DO_2crit, as evidenced by elevated lactate levels, should be rapidly evaluated for the best means to improve tissue DO_2. Assuming hemoglobin oxygen saturations above 90%, apart from increasing CaO_2 by transfusion, is there an opportunity to increase global DO_2 by increasing cardiac output by increasing preload or decreasing afterload? In terms of the microvasculature can guided vasodilation be used to improve tissue DO_2? These patients will also have tissue oxygen or carbon dioxide indices of decreased tissue oxygen delivery. Using such monitoring will assist in understanding how rapidly transfusion, or other means, to increase DO_2 are working. Monitoring will also assist in understanding just how far above DO_2crit the patient is after any intervention. For example, if a patient is transfused resulting in clearance of lactate, but tissue oxygen saturation is still 40% (normal 65% to 75%) then the patient is likely to be just above DO_2crit and any additional insult or metabolic requirement may push them back to delivery dependent consumption. Lastly, is there an opportunity to decrease VO_2? Is the patient febrile, what is the assumed work of breathing (does the patient require intubation?), is the patient in pain and requiring analgesia? Attention to all of these factors in a given situation can drastically reduce VO_2 thus bringing it more in line with available DO_2.
3. For patients who are anemic but not symptomatic or past their DO_2crit, what level of oxygen extraction should be tolerated prior to transfusion? As discussed earlier, oxygen and carbon dioxide monitoring technologies can be useful as a means to examine tissue oxygen extraction as a preDO_2crit indicator of the adequacy of tissue oxygen delivery. This is where decision making becomes problematic and will rely on art. If for example, muscle or oral tissue oxygen saturation is 40%, this patient is likely hovering close to DO_2crit and has evidence of maximum oxygen extraction in the face of decreased delivery. How long does the clinician believe the patient can keep up such extraction before DO_2crit is reached? Can extraction be reduced by increasing DO_2 by means other than transfusion? Other mitigating factors such as respiratory or central cardiovascular status should be taken into account. For example, patients with evidence of increased extraction who are in the process of ventilator weaning and who will incur a higher work of breathing once extubated might require transfusion in the face of an already elevated oxygen extraction ratio.

Again, all factors should be taken into account. In reality, however, the majority of transfusion decisions in medicine are not based on either patient symptoms or markers of oxygen transport. Table 5.1 provides some guidelines for the use of tissue oxygenation parameters.

TABLE 5.1
TRANSFUSION MONITORING END-POINTS

Global End-Points	
Hemoglobin:	?
Lactate:	<2.0 mm
SaO_2:	94%–99%
$ScvO_2/SvO_2$:	70%–80%
VO_2:	>90 mL/min/m^2
Tissue-Specific End-Points	
pHi:	>7.32
$PgCO_2$–$PaCO_2$ gap:	<15 mm Hg
$PgCO_2$–$PetCO_2$ gap:	<15 mm Hg
$PslCO_2$–$PaCO_2$ gap:	<15 mm Hg
$PslCO_2$–$PetCO_2$ gap:	<15 mm Hg
StO_2:	>65% (skeletal muscle, brain, or GI tract)

SUMMARY

A better basic understanding of the principle of oxygen transport and means by which to monitor oxygenation at the tissue level are required before significant changes in transfusion practice can be expected. The routine transfusion of red blood cells in the setting where no evidence of central organ dysfunction, tissue dysoxia, or significantly enhanced oxygen extraction exists cannot be rationally supported from a physiologic perspective. Treating red blood cell transfusion as a resuscitative modality and using appropriate resuscitative monitoring end-points may significantly reduce transfusion requirements. Future clinical trials using these principals are warranted.

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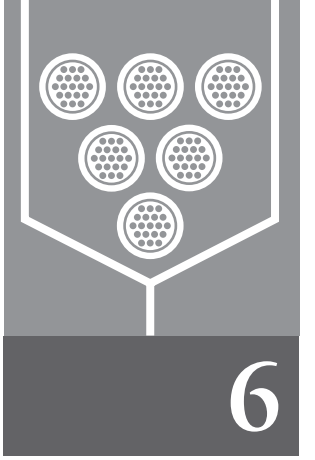

6

Physiology of Anemia and Red Blood Cell Transfusion

Howard L. Corwin ***Paul C. Hébert***

Red blood cell (RBC) transfusions date back to the mid 17th century, however it was not until the early part of the 20th century that RBC transfusion became a mainstay of clinical practice (1). Historically a hemoglobin of 10 g per dL and a hematocrit of 30% have been the generally accepted minimum levels, particularly in the surgical setting. First proposed in 1942, the "10/30" rule has become accepted over the years as the appropriate "transfusion trigger," more as a matter of preference than of data (2). The value of RBC transfusion in clinical practice as the treatment for anemia was unchallenged through most of this century (1). However, in the early 1980s, transfusion practice began to come under systematic scrutiny, including critical examination of transfusion risks and efficacy (3–5). More recent guidelines now advocate empiric automatic transfusion thresholds in favor of a practice of blood transfusion only for defined physiologic need, despite being difficult to define (3,4). Many of the physiological concepts in oxygen (O_2) transport and utilization were described in the early part of the 20th century and are still widely accepted (6). This chapter will review the basic principles of oxygen transport and focus on the physiological consequences of anemia and efficacy of red blood cell (RBC) transfusion.

OXYGEN TRANSPORT

Hemoglobin is a complex molecule consisting of four globin moieties, each incorporating an iron containing heme ring where oxygen may bind. The O_2 carrying capacity of hemoglobin, or binding affinity to O_2, is represented by a sinusoidal relationship between the hemoglobin saturation and the partial pressure of oxygen (pO_2). This relationship, referred to as the oxyhemoglobin dissociation curve, enables both efficient loading in the lungs at high pO_2s and efficient unloading in the tissues at low pO_2 values. However, hemoglobin's O_2 binding affinity (the degree to which O_2 molecules saturate the hemoglobin binding sites at a given pO_2) may be altered by various disease states and may play a significant adaptive role in response to anemia. The amount of O_2 delivered, either to the whole body or to specific organs, is the product of blood flow and arterial O_2 content. For the whole body, O_2 delivery (DO_2) is the product of total blood flow or cardiac output (CO) and arterial O_2 content (CaO_2). Thus, the equation reads:

$$DO_2 = CO \times CaO_2 \quad (1)$$

When breathing ambient air under normal conditions, O_2 present in arterial blood is transported by hemoglobin which is nearly fully saturated, while the remainder is dissolved in plasma water. The negligible amount of dissolved O_2 is directly proportional to the partial pressure and may be calculated by multiplying pO_2 by a constant (k = 0.00301), termed the solubility coefficient. Thus, under most circumstances, arterial O_2 content may be approximated from the portion bound to hemoglobin using the equation:

$$CaO_2 \text{ (in mL/L)} = \% \text{ Sat} \times 1.39 \text{ (mL/g)} \times [\text{Hb}] \text{ (g/dL)} \quad (2)$$

If CaO_2 is substituted from equation 2 into 1, then:

$$DO_2 = CO \times (\%Sat \times 1.39 \times [Hb]) \quad (3)$$

where CO = cardiac output in L/min, %Sat = hemoglobin O_2 saturation in %, [Hb] = hemoglobin concentration in g/dL and 1.39 is the hemoglobin binding constant (i.e., 1.39 mL of O_2 will bind to 1g of hemoglobin when fully saturated).

Cardiac output, a measure of blood flow to the entire body, is the other major determinant of O_2 delivery. It may be quantified by multiplying the stroke volume (the difference between end diastolic volume and end systolic volume in liters) and heart rate (in beats per minute). Stroke volume is influenced by preload (end diastolic volume), afterload (the arterial pressure and resistance encountered during each ventricular ejection), and contractility (the force generated during each contraction). Cardiac work or energy expended by the heart is directly proportional to the heart rate, the change in pressure (arterial—left ventricular pressure) and volume (ejection fraction) during a cardiac cycle (7–12). Thus, for a given blood pressure, increasing cardiac output will increase myocardial O_2 consumption or for a given cardiac output, O_2 consumption will also increase with increased blood pressure. A tight coupling of myocardial O_2 supply to O_2 demand is regulated by metabolic byproducts such as adenosine (13).

Tissue hypoxia (and anoxia) will occur if O_2 delivery is decreased to a level where tissues no longer have enough O_2 to meet their metabolic demands. From Equations 1 and 3 above, it is apparent that tissue hypoxia may be caused by decreased O_2 delivery due to decreases in hemoglobin concentration (anemic hypoxia), cardiac output (stagnant hypoxia), or hemoglobin saturation (hypoxic hypoxia). Each of the determinants of DO_2 has substantial physiologic reserves thereby enabling the human body to adapt to significant increases in O_2 requirements or decreases in one of the determinants of DO_2 as a result of various diseases.

In health, the amount of O_2 delivered to the whole body exceeds resting O_2 requirements by a factor of twofold to fourfold. For example, if we assume a hemoglobin level of 15.0 g per dL, an oxygen saturation (% sat) of 99%, and cardiac output of 5 liters per minute, then O_2 delivery will be 1032 mL per min. At rest, the amount of O_2 required or consumed by the whole body will range from 200 to 300 mL per min. An isolated decrease in hemoglobin concentration to 10.0 g per dL will result in an O_2 delivery of 688 mL per min. Despite this 33% decrease in O_2 delivery, there remains a twofold excess of O_2 delivery as compared to O_2 consumption. However, a further drop in hemoglobin concentration to 5.0 g per dL with all other parameters, including cardiac output, remaining constant will decrease O_2 delivery to a critical level of 342 mL per min. Under stable experimental conditions, this dramatic decrease O_2 delivery would not have affected O_2 consumption. However, below a critical level or threshold of O_2 (DO_2crit), O_2 consumption will decrease with further decreases in hemoglobin concentrations (and decreased O_2 delivery). Therefore a biphasic relationship between oxygen delivery and consumption exists; an O_2 delivery-independent portion of the relationship above a threshold value (DO_2crit), where O_2 consumption is independent of O_2 delivery and a delivery-dependent or supply-dependent portion, where O_2 delivery is linearly related to O_2 consumption. The latter portion of this relationship below the DO_2crit indicates the presence of tissue hypoxia. Both laboratory and clinical studies have attempted to determine DO_2crit. The most rigorous clinical study (14) found a threshold value of 4 mL/min/kg while other clinical and laboratory studies found value in the range of 8 mL/min/kg (15–17). The DO_2crit, or the anaerobic threshold, is unlikely to be a single fixed value but will vary substantially depending on such factors as basal metabolic rate, the specific organ or tissue, some disease states, and perhaps complex factors such as a patient's age or genetic make-up.

Once blood is oxygenated, it is distributed to all organs and tissues through the arterial tree into the microcirculation. Organ blood flow is controlled by arterial tone in medium size vessels, primarily responsive to changes in autonomic stimulation and the release of locally generated vasodilating substances. Within organ systems, red cells are carried into the microcirculation where O_2 is released to the tissues through a thin-walled capillary network. Once released, O_2 diffuses through the interstitial space finally finding its way into the cell and mitochondria to be used in cellular respiration. There are additional adaptive changes in the microcirculation enhancing O_2 delivery in anemic states (6).

Adaptation to Anemia

In anemia, O_2 carrying capacity is decreased but tissue oxygenation is preserved at hemoglobin levels well below 10.0 g per dL. Following the development of anemia, adaptive changes include a shift in the oxyhemoglobin dissociation curve, hemodynamic alterations, and microcirculatory alterations. The shift to the right of the oxyhemoglobin dissociation curve in anemia is primarily the result of increased synthesis of 2,3 diphosphoglycerate (2,3-DPG) in red cells (18–24). This rightward shift enables more O_2 to be released to the tissues at a given pO_2, offsetting the effect of reduced O_2 carrying capacity of the blood.

Several hemodynamic alterations also occur following the development of anemia. The most important determinant of cardiovascular response is the patient's volume

status or more specifically, left ventricular preload. The combined effect of hypovolemia and anemia often occur as a result of blood loss. Acute anemia thus may cause tissue hypoxia or anoxia through both decreased blood flow (stagnant hypoxia) and decreased O_2 carrying capacity (anemic hypoxia) (6,25–27).

The body primarily attempts to preserve O_2 delivery to vital organs through increased cardiac output as well as increased arterial and venous vascular tone mediated through increased sympathetic tone. In addition, central and regional reflexes redistribute organ blood flow. The adrenergic system plays an important role in altering blood flow to, and within, specific organs. The renin–angiotensin–aldosterone hormone system is also stimulated to retain both water and sodium. Losses ranging from 5% to 15% in blood volume result in variable increases in resting heart rate and diastolic blood pressure measures. Orthostatic hypotension is often a sensitive indicator of relatively small losses in blood volume which are not sufficient to cause a marked blood pressure fall. Larger losses will result in progressive increases in heart rate and decreases in arterial blood pressure accompanied by evidence of end-organ hypoperfusion. The increased sympathetic tone diverts decreasing cardiac output away from the splanchnic, skeletal, and skin circulation toward the coronary and cerebral circulation. The cardiovascular and systemic responses to acute blood loss are not simply a result of the amount of volume lost but are thought to be modified by patient characteristics such as age, co-morbid illnesses, preexisting volume status and hemoglobin values, as well as the rapidity of blood loss.

The compensatory changes in cardiac output have been the most thoroughly studied cardiovascular consequence of normovolemic anemia. When intravascular volume is stable or increased following the development of anemia (as opposed to hypovolemic anemia and shock), increases in cardiac output have been consistently reported. Indeed, an inverse relationship between hemoglobin levels (or hematocrit) and cardiac output has been clearly established in well controlled laboratory studies (28–31). In a variety of clinical settings similar observations have been made (28,32–39). Reported thresholds for this phenomenen identified in primary clinical and laboratory studies have ranged from 7.0 to 12.0 g per dL (39–43).

Two major mechanisms are thought to primarily modulate the physiological processes underlying the increased cardiac output during normovolemic anemia: (a) reduced blood viscosity and (b) increased sympathetic stimulation of the cardiovascular effectors (6,44–46). Blood viscosity exerts major effects on both preload and afterload, two of the major determinants of cardiac output (44,47,48) while sympathetic stimulation primarily increases the two other determinants, heart rate, and contractility. As opposed to hypovolemic anemia, the effects of blood viscosity appear to predominate in this setting (47–49).

EFFICACY OF RED BLOOD CELL TRANSFUSION

Maximizing oxygen delivery and oxygen consumption in critically ill patients has generated a great deal of interest over the last two decades. This approach was initially raised as a result of studies by Shoemaker et al., suggesting that supranormal levels of oxygen delivery and oxygen utilization in critically ill surgical patients were associated with improved clinical outcomes (50–53). However, subsequent prospective randomized trials (54,55) and a recent meta-analysis (56) have failed to confirm the benefit of achieving supranormal values of oxygen delivery and oxygen utilization and have raised the possibility that this strategy may in fact result in worse clinical outcomes and increased mortality.

Red blood cell (RBC) transfusions are commonly utilized in an attempt to increase oxygen delivery to the tissues and in turn improve tissue oxygenation, especially in shock states. The rationale for this therapeutic approach is that an increase in hemoglobin will increase the oxygen carrying capacity of blood and thus provide more oxygen delivery to delivery-dependent tissue. However, stored RBCs have a low p50 that increases the affinity of hemoglobin for oxygen and thereby reduces oxygen release to tissues (shift oxygen dissociation curve to the left). Furthermore, standard CPD-stored blood is rapidly depleted of 2,3 diphosphoglycerate (2,3, DPG) and ATP, with resultant inadequacy of the red cell oxygen transport function.

Studies regarding the efficacy of RBC transfusions to increase tissue oxygen consumption and to improve microcirculation have yielded conflicting results. Clinical studies have not consistently demonstrated that this therapeutic maneuver is accompanied by an increase in oxygen utilization at either the whole body level or at the individual organ level. While a number of clinical studies have evaluated hemodynamic and oxygen transport parameters before and after RBC transfusion in critically ill patients, few studies have demonstrated a significant improvement in these variables after RBC transfusion (57–60).

Are there some subgroups of critically ill patients that may respond favorably to RBC transfusion? Red blood cell (RBC) transfusion is commonly used to increase oxygen transport in patients with sepsis and other shock states. The expected benefit from RBC transfusion is to immediately improve oxygen delivery, and thus prevent cellular

injury. The question regarding whether RBC transfusion improves regional microcirculation is important, since the goal of resuscitation is to improve organ perfusion and prevent organ failure. Conrad et al. (61) investigated the effect of increasing oxygen delivery (DO_2) through an isolated increase in arterial oxygen content by RBC transfusion following adequate fluid resuscitation from septic shock in human. Despite the increase in oxygen delivery, there was no increase in oxygen consumption (VO_2) or decrease in lactate. Subset analysis documented that patients with a low pretransfusion oxygen extraction ratio (less than 24%) had a significant increase in oxygen consumption with blood transfusion. On the other hand, in a study in of septic patients (62), RBC transfusion in septic patients with an increased pretransfusion serum lactic acid, despite increased DO_2, the VO_2 was not significantly increased after RBC transfusion. It has also been noted that increasing O_2 delivery with dobutamine, as opposed to RBC transfusions, is more effective in reversing gastric intramucosal acidosis (63). Additional studies have documented the efficacy of dobutamine in improving splanchnic perfusion and splanchnic oxygen deliver in critically ill patients (64).

Transfused RBCs, especially during the time period immediately following transfusion, are not normal. Storage of RBCs temporarily decreases 2,3 DPG levels, interfering with the ability of RBCs to unload oxygen, and impairing RBC deformability. The duration of storage may also be an important determinant of the efficacy of RBCs. Marik and Sibald (65) examined the effect of RBC transfusion on gastrointestinal and whole body oxygen uptake in septic patients. There was no increase in systemic oxygen uptake measured by indirect calorimetry in any of the patients studied for up to 6 hours posttransfusion (including those patients with an elevated arterial lactate concentration). Interestingly, a significant inverse association between the change in gastric intramucosal pH and the age of the transfused blood was observed. In those patients receiving blood that had been stored for more than 15 days, the gastric intramucosal pH consistently decreased following the RBC transfusion. The authors postulated that the poorly deformable transfused RBCs cause micro-circulatory occlusion in some organs, which may lead to tissue ischemia in some organs. A follow-up study employing a rat sepsis model demonstrated that transfusion of fresh RBCs cells (stored for 3 days in citrate phosphate dextrose adenine-1) acutely increased systemic oxygen uptake in delivery-dependent animals, whereas transfusion of RBCs stored for 28 days failed to improve tissue oxygenation (66). In contrast to this, Walsh et al. (66a) evaluated changes in gastric intramucosal pH (pHi), a measure of gastric perfusion, in 22 mechanically ventilated, critically ill patients who required a red cell transfusion. In this study, the authors were not able to detect any adverse consequences on pHi and changes in the arterial-gastric mucosal CO_2 gap with a storage time exceeding 20 days as compared to patients receiving red cells less than 5 days. A recent study has shown that the average age of RBCs transfused in the United States is 21 days (67).

The influence of storage on RBC rheological properties has been examined in detail by a number of investigators (68–70). Studies have documented that significant alterations of RBC shape begin in the second week of storage and continue to progress during the remainder of the storage period. RBC shape changes are accompanied by a progressive decrease in the deformability index and an increase in both hemolysis and acidosis. Transfusion of packed RBC older than 7 days may contribute to hemorrheological disorders in critically ill patients (68). Furthermore, RBC storage induces changes that are associated with an increase in RBC aggregability (70). This potential to increase aggregation should be taken into account when blood transfusion is considered, particularly for patients with micro-circulatory disorders, such as critically ill patients.

In stored blood preparations, it has also been documented that free hemoglobin and polymorphonuclear leukocyte elastase concentrations increase significantly with storage time, with resultant increased hemolysis of RBCs (71). A recent hypothesis has emerged regarding the adverse effect of transfusion of stored blood. Cell free ferrous hemoglobin in the plasma, after transfusion of stored blood, rapidly destroys nitric oxide by oxidation to methemoglobin and nitrate. Nitric oxide reacts at least 1,000 times more rapidly with free hemoglobin than with erythrocytes. Limited nitric oxide bioavailability promotes regional and systemic vasoconstriction and subsequent organ dysfunction (72,73).

It has been suggested that blood transfusion is a risk factor for the development of multiple organ failure and worse outcome in trauma and surgical patients (74,75). One hypothesis is that stored RBCs (>14 days) can prime PMNs and thereby provoke multiple organ failure. A recent in vitro study plasma from day 42 RBCs stimulated significant PMN release of both IL-8 and secretory phospholipase A2 as compared to both control and plasma from fresh (day 0) RBCs (76). Transfused blood is therefore emerging as an inflammatory agent that is capable of producing PMN priming which may promote organ dysfunction.

In summary, does prolonged RBC storage lead to adverse clinical consequences? As noted above, laboratory evidence suggests that prolonged red cell storage may be deleterious and the observational studies report a number of associations with adverse clinical outcomes such as

mortality and organ failure. However, only two small adult trials have been reported on the clinical consequences of prolonged red cell storage (65,66a). Given the limited evidence and the potential importance of the question additional studies are required to definitively address the issue.

HOW MUCH HEMOGLOBIN IS ENOUGH?

There is evidence that low levels of hemoglobin can be tolerated in healthy subjects. Hematocrits of 10% to 20% have been achieved in both dogs and baboons using normovolemic hemodilution without untoward effects to the animals (77,78). Similarly, studies in patients with preserved left ventricular function undergoing coronary artery bypass grafting demonstrated that hemodilution to a target hematocrit of 15% was well tolerated (79,80). Weiskopf et al. (81) induced normovolemic hemodilutional anemia to hemoglobin levels of 5 grams per dL in healthy human patients prior to surgery as well as normal volunteers. They found no evidence for reduced oxygen delivery associated with acute anemia (81). Rawstron compared surgical patients with preoperative hemoglobin levels >10 grams per dL to patients with preoperative hemoglobin levels <10 grams per dL, and found no difference in postoperative complications (82).

A wealth of data regarding the impact of anemia on surgical outcome comes from studies of Jehovah's Witness patients. Carson et al. observed 125 Jehovah's Witness patients undergoing surgery, no patient with a hemoglobin >8 grams per dL and blood loss <500 mL died in this series (83). In a study of elective surgery in 107 Jehovah's Witness patients, Spence et al. noted that mortality was related more to blood loss than preoperative hemoglobin (84). They observed that surgery was safely performed in patients with hemoglobin levels as low as 6 grams per dL, providing blood loss was less than 500 mL. Kitchens has summarized the published experience in Jehovah's Witness patients undergoing major surgery (79). A 1.4% mortality rate attributable to anemia was observed among 1,404 patients. Ninety percent of these deaths were in patients undergoing cardiovascular operations.

It seems clear that hemoglobin levels falling significantly below the "10/30" threshold can be tolerated by individuals who are not critically ill. However, is this applicable to the critically ill patient population? The best evidence available regarding the efficacy of blood transfusion among critically ill patients is the randomized controlled trial by Hébert et al (85). They compared a liberal transfusion strategy (hemoglobin 10 to 12 grams per dL) to a restrictive transfusion strategy (hemoglobin 7.0 to 9.0 grams per dL). Patients in the liberal transfusion arm received significantly more RBC transfusions. Overall in-hospital mortality was significantly lower in the restrictive strategy group, although the 30-day mortality rate was not significantly different. However, in those patients who were less ill (APACHE <20) or younger (<55 years of age) the 30-day mortality rates were significantly lower for the patients in the restrictive transfusion group. Therefore, a restrictive strategy is at least equivalent and possibly superior, in some patients, to a more liberal transfusion strategy.

On the other hand it has been suggested that patients with cardiovascular disease may experience increased risk of morbidity and mortality when exposed to anemia. Carson et al. studied the risk of death and morbidity among 1,958 noncardiac surgical Jehovah's Witness patients (86). They found that both a low preoperative hematocrit and a substantial blood loss increased the risk of serious morbidity or death. The effect was significantly more pronounced among patients with cardiovascular disease. They concluded that even mild anemia is associated with increased risk of mortality and that patients with cardiovascular disease have a substantially higher risk. Hardy et al. studied the association between the nadir hemoglobin in the 24 hours after surgery and major morbidity among 2,664 cardiac surgical patients (87). They found that the lower minimum hemoglobin concentration was associated with increased hemodynamic instability and renal failure. However, RBC transfusion did not appear to reduce morbidity. In another study of high risk patients undergoing arterial bypass procedures, Nelson et al. found that a postoperative hematocrit of <28 percent was significantly associated with increased myocardial ischemia and morbid cardiac events (88). It has been suggested that in high risk vascular surgery patients with impaired ventricular function, the lack of a compensatory increase in cardiac output leaves blood transfusion as the only means to increase oxygen delivery postoperatively (89). These authors suggest hemoglobin levels of 10 to 12 g per dL. Similarly, patients with cardiac disease undergoing radical prostatectomy had a higher incidence of perioperative ischemic events if anemic (90). This was particularly apparent in the setting of tachycardia.

Patients undergoing cardiopulmonary bypass usually experience hemdilutional anemia because the pump is primed with some combination of crystalloid and colloid solutions. Among patients with atherosclerotic coronary vascular disease and preserved left ventricular function undergoing coronary artery bypass grafting, hemodilution to a target hematocrit of 15% was well tolerated (91,92). This conclusion was based upon the observation that there was no evidence of myocardial ischemia and that tissue uptake and utilization of oxygen was not impaired.

However, two studies from prospective observational cardiac surgical databases have reported the association of hemodilutional anemia and increased mortality during cardiopulmonary bypass for CABG surgery. Fang et al. observed that a lowest hematocrit during cardiopulmonary bypass (CPB) (less than 14% for low risk patients and less than 17% for high risk patients) was an independent risk factor for mortality among 2,738 consecutive isolated CABG patients (93). The Northern New England Cardiovascular Study Group recently reported that lowest hematocrit during CPB was significantly associated with increased in-hospital mortality, need for intra-aortic balloon pump counter-pulsation, and return to cardiopulmonary bypass after initial separation among 6,980 consecutive isolated CABG patients (94). This study identified that smaller patients and those with lower preoperative hematocrit are at higher risk of low hematocrit during CPB. The association of lowest hematocrit during CPB and increased risk of acute renal dysfunction was also observed (95). None of these studies examined transfusion, only low hematocrit.

Several recent studies have examined transfusion practice in patients with acute cardiac disease. Hébert et al. reported results from the subgroup critically ill patients who had cardiovascular disease (96), from their randomized trial comparing a restrictive transfusion strategy to a liberal transfusion strategy (85). They found no significant difference in mortality between the two transfusion strategies in patients with cardiovascular disease in general. However, in the patients with severe ischemic heart disease, a trend towards decreased survival was observed in the group managed with the restrictive strategy. This was the only subgroup in the study that favored the liberal transfusion strategy. Wu et al. (97) retrospectively studied Medicare records of 78,974 patients older than age 65 who were hospitalized with a primary diagnosis of acute myocardial infarction. Lower admission hematocrit values were associated with increased 30-day mortality with a mortality rate approaching 50% among patients with a hematocrit of 27% or lower who did not receive a RBC transfusion. Interestingly, RBC transfusion was associated with a reduction in 30-day mortality for patients who received at least 1 RBC transfusion if their admitting hematocrit was less than 33% while RBC transfusion was associated with increased 30-day mortality for patients whose admitting hematocrit values were 36.1% or higher. Rao et al. (98) analyzed the effect of RBC transfusion on outcome in over 24,000 patients with acute coronary syndrome that had been enrolled in three clinical trials. This post hoc analysis found that RBC transfusion in patients with acute coronary syndrome and a nadir hematocrit greater than 25 was associated with an increase in 30-day mortality, which persisted after adjusting for comorbidities. The data currently available does not allow firm conclusions to be made regarding transfusion in the patient with cardiac disease. Further studies are required before definitive recommendation regarding anemia and transfusion practice in patients with cardiac disease can be made.

Finally, when considering the efficacy of RBC transfusion and making decisions on RBC transfusion, it should be kept in mind that RBC transfusion is not without risk. This is particularly important given the questions regarding transfusion efficacy which have been raised. The two recent large observational trials (ABC and CRIT studies), which combined included over 8,000 patients, observed that RBC transfusion was independently associated with worse clinical outcomes (67,99). These observational studies, as well as the studies by Hébert et al. and others (85,96) have raised questions regarding the validity of the historic assumption that RBC transfusion is beneficial for critically ill patients with anemia.

CONCLUSION

It is clear from the physiologic data available that the body is able to adapt to anemia. The most important adaptive responses from a physiological standpoint involve the cardiovascular system, consisting in particular of elevation of the cardiac output and its redistribution to favor the coronary and cerebral circulations, at the expense of the splanchnic vascular beds. On the other hand, there is a remarkable lack of clinical studies addressing how normal physiological adaptive responses may be affected by a variety of diseases and conditions which often accompany and may complicate anemia, and interactions with other coexisting clinical variables.

In view of the lack of firm evidence on the interactions of concurrent diseases and anemia in various patient populations, understanding the physiological consequences of anemia, while important, may still not be fully sufficient to provide firm and rational guidance to transfusion practice in specific complex clinical instances. From the brief review of physiological principles it is evident that cardiac function must be a central consideration in decisions regarding transfusion in anemia. Particular attention needs to be paid to the possible presence of coronary artery disease, or incipient or cardiac failure, as these conditions may require careful transfusions to improve oxygen delivery at levels which may not necessitate such interventions when cardiac disease is absent.

At this point in time, additional clinical and experimental investigation is required to develop rational and comprehensive guidelines. Prudent and conservative management, based on awareness of risks and sound understanding of the

normal and pathological physiology must remain the guiding principle. The best data available would suggest that most patients can tolerate hemoglobin levels in the 7 to 9 g per dL range without suffering adverse consequences related to the anemia. Patients with acute cardiac disease may require higher hemoglobin levels, however more data is required. Routine use of RBC transfusion in the absence of a clear physiologic indication is associated with clear risk and at best limited efficacy.

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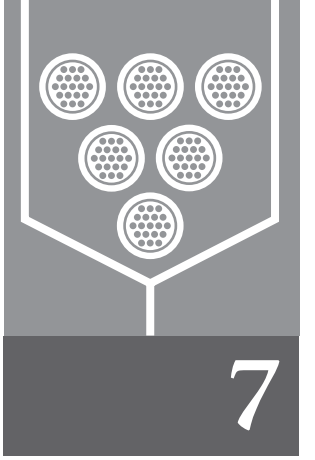

7

Physiology of Hemostasis

Wayne L. Chandler

The purpose of this chapter is to describe the different parts of the hemostatic system with an orientation toward the practicing surgeon and anesthesiologist. Our understanding of how hemostasis is regulated in vivo has changed substantially over the last 10 years and part of the goal of this chapter is to bring some of these new concepts relating to the control of hemostasis to clinical practice. The separation of the intrinsic and extrinsic coagulation systems is now realized to be artificial. In vivo only a single coagulation pathway exists. The research focus is now on cell activation and signaling systems and the regulation of hemostatic factor activation. New medications have been developed to both enhance and suppress clotting. While this chapter is not intended as a review of new medications, they will be briefly described throughout the text to highlight both the function of the drug and clinically relevant aspects of hemostatic regulation. While sufficient details of the hemostatic system are given to aid in understanding how the system works and the clinical relevance of the different parts, this chapter is not intended as a detailed review of the gene structure or molecular biology of the individual proteins, subsystems, or cells involved in hemostasis.

Many techniques control bleeding from larger blood vessels where the relatively high pressure and large volume of blood flow require temporary clamping, ligature, or some other mechanical occlusion to stop the flow of blood. At the other end of the size distribution of blood vessels, the microvasculature, individual arterioles and venules cannot be tied off; the hemostatic system must stop bleeding and maintain hemostasis for the 10 to 14 days necessary for the wound to heal. Whenever the vascular system is injured, the hemostatic system must accomplish two goals: plugging the hole while keeping the majority of vessels open and the blood flowing. To do this the hemostatic system is designed to rapidly generate a clot at the site of vascular injury, limit the size of the clot to the minimum necessary to stop bleeding, while blocking hemostatic activation and clot formation throughout the remainder of the vascular system. Two important questions will be considered: how is the hemostatic plug formed after vascular injury and why does the blood ordinarily not clot within the vasculature?

The next section is a quick overview of the hemostatic system as it is presently understood, followed by detailed descriptions of platelets, the coagulation system, endothelial cells and the regulation of hemostasis, fibrinolysis, and wound healing with a brief section on alterations in hemostasis. Each of the detailed sections contains a brief description of the important proteins and cells involved in that system, the normal regulation of the system, and examples of how it can be altered in disease and through medication.

BRIEF OVERVIEW OF HEMOSTASIS

Healthy blood vessels are lined by endothelial cells that provide a smooth surface for the blood to flow over, express proteins, and secrete substances that prevent clot formation and prevent platelets and coagulation proteins from coming in contact with subendothelial proteins that simulate hemostatic activation (1). The first response to injury in vessels with muscular walls is contraction to limit blood loss. In all vessels, injury or disruption of the endothelium lining the blood vessel results in exposure of subendothelial

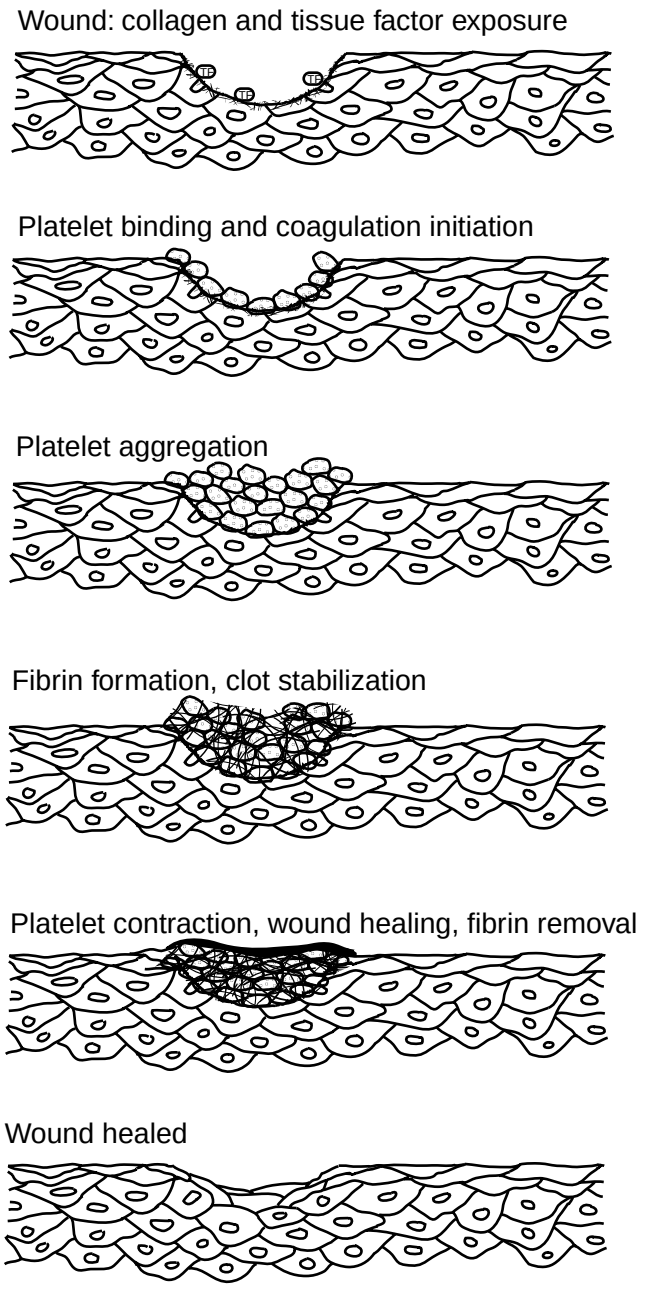

Figure 7.1 Major steps of hemostasis using a cutaneous wound as an example.

proteins such as collagen and tissue factor, that activate platelets and the coagulation system (Fig. 7.1).

Formation of a platelet plug is the first step in hemostasis. The sequence of forming a platelet plug occurs in three steps: adhesion of platelets to subendothelial tissue, activation of the adherent platelets, and activation and aggregation of other platelets to complete the hemostatic plug. Platelets in blood flowing past exposed subendothelial collagen adhere to the collagen through von Willebrand factor. Adhesion of platelets to a wound results in a monolayer of platelets that anchors the forming platelet plug to the tissue. Next, platelets are activated through the binding of various molecules to membrane receptor proteins. A variety of different platelet activators have been described (Fig. 7.2). Some are proteins (e.g., collagen, von Willebrand factor, and thrombin), whereas others are small molecules (e.g., ADP, serotonin, and epinephrine). Platelets encounter them in several ways. Some, such as collagen or thrombin, are external to platelets; whereas others, such as ADP or serotonin, are stored in platelet granules and released upon activation. The activation step, on the one hand, causes the expression on the platelet membrane of fibrinogen binding sites, resulting in aggregation, and on the other stimulates the secretion from the activated platelets of additional activating molecules (agonists) that recruit more platelets to the growing aggregate. The first platelets to adhere to the wound are activated by binding to collagen, these activated platelets in turn release granules that activate additional platelets and accelerate the coagulation system.

Simultaneous with platelet adhesion, activation, and aggregation, exposure of tissue factor activates the coagulation system (Fig. 7.3). Tissue factor accelerates the activation of factor VII, which in turn activates factor IX. Activated factor IXa binds along with VIIIa to the activated platelet surface forming an enzyme complex that activates factor X (tenase). Activated factor Xa binds along with Va to the activated platelet surface forming a second enzyme complex that activates prothrombin to thrombin (prothrombinase). Thrombin converts fibrinogen to fibrin, which polymerizes forming a strong protein matrix over platelets. Fibrin is cross-linked by factor XIIIa stabilizing the clot.

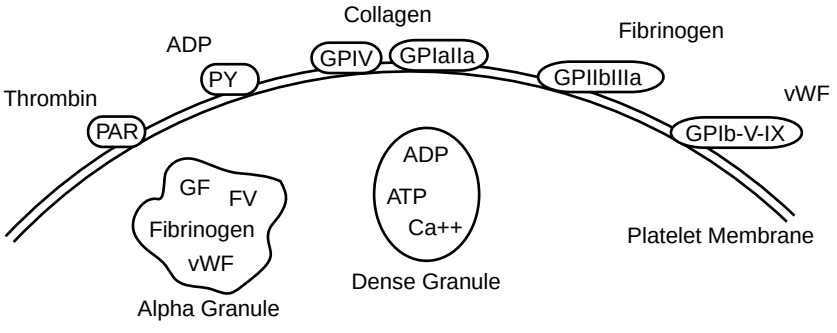

Figure 7.2 Diagram of the platelet surface showing some of the major platelet ligands that stimulate platelet adhesion (collagen; vWF, von Willebrand factor), platelet activation (thrombin, ADP, collagen), and platelet aggregation (fibrinogen), their associated receptors on the platelet surface (PAR, protease activated receptor), and some of the contents of the platelet alpha granule (GF, growth factor; FV, factor V) and dense granule that are released after platelet activation.

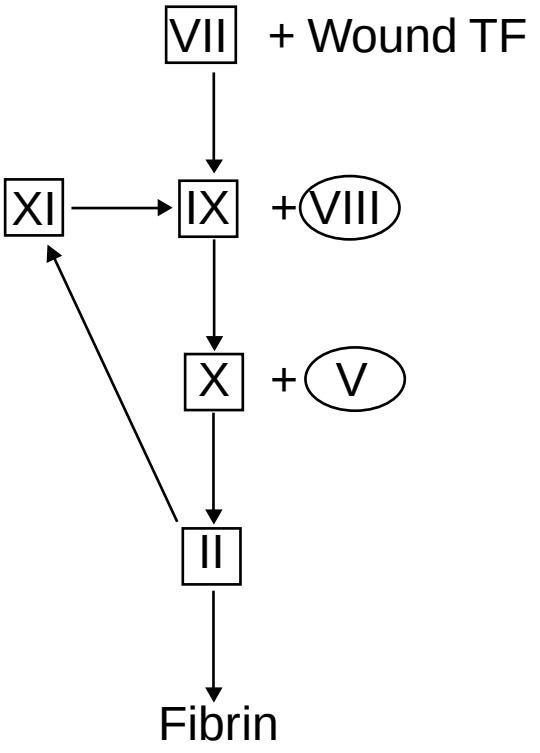

Figure 7.3 Diagram of the coagulation system in vivo. Coagulation is initiated by the exposure or transport of tissue factor to the site of the wound. Tissue factor helps activate factor VII to VIIa which in turn activates factor IX to IXa. Factor IXa binds with factor VIIIa to the platelet surface where it activates factor X to Xa. Factor Xa binds with factor Va to the platelet surface where it converts prothrombin into thrombin. Thrombin has many functions including activation of platelets and the cofactors V and VIII, conversion of fibrinogen into fibrin which forms the meshwork over the platelet plug, activation of factor XI to XIa which helps sustain factor IX activation, and finally activation of factor XIII which cross-links fibrin increasing the strength and stability of the clot. Active proteolytic enzymes have a box around the name; cofactors have an oval around the name.

Both platelets and the coagulation system are characterized by amplifying reactions triggered by a small external stimulus, ultimately leading to rapid hemostatic clot formation. Collagen binds and activates platelets (triggering reaction). Activated platelets release substances that activate other platelets leading to aggregation and platelet plug formation (amplifying reactions). Tissue factor binds and accelerates activation of factor VII (triggering reaction). Activated factor VIIa initiates the activation of a series of enzymes in the coagulation system (amplifying reactions) eventually leading to formation of fibrin and a stable clot. The two systems, platelets and coagulation, influence each other and wound healing as well: by expression on the platelet surface of high affinity binding sites for coagulation factors, platelets provide a catalytic surface that greatly promotes the rate of thrombin generation and clot formation, by the release of growth factors; platelets play an important role in initiating angiogenesis and wound healing, while thrombin generated by the coagulation system in turn is a powerful activator of platelets.

So far we have described the processes that stimulate clot formation at the site of the wound. Equally important are the processes that prevent vascular occlusion (thrombosis) either at the site of the wound or downstream. If left unchecked, thrombin and other active coagulation factors would stimulate clot formation in other undamaged areas of the vascular system. Healthy undamaged endothelial cells destroy activated coagulation factors through three systems: (a) tissue factor pathway inhibitor (TFPI) in conjunction with activated factor X inhibits VIIa-tissue factor complexes, (b) antithrombin bound to endothelial heparan sulfate inhibits activated factors IXa, Xa, XIa and thrombin, and (c) the protein C system destroys activated cofactors Va and VIIIa. Lastly, the fibrinolytic system plays an important role in limiting the size of the clot. Tissue plasminogen activator (tPA) secreted by endothelial cells binds to fibrin where it converts plasminogen to plasmin which lyses or dissolves the clot. The dynamic interplay of fibrin formation by the coagulation system versus fibrin degradation by the fibrinolytic system controls the size of the thrombus, making sure it is adequate to maintain hemostasis but not so large as to occlude the vessel.

Hemostasis is just the beginning of the wound healing process. Once bleeding is stopped, growth factors released by platelets and other factors generated by the coagulation and complement systems attract and activate macrophages and fibroblasts. Neutrophils cleanse the wound, endothelial and epithelial cells cover the clot, new vessels grow into the wound, collagen is formed, fibrin is removed, and the wound heals (2).

PLATELETS

Platelets are small nonnucleated cells derived from megakaryocytes and released from the bone marrow by budding off fragments of megakaryocyte cytoplasm. Production of platelets is regulated by the growth factor thrombopoietin along with other cytokines and factors in blood (3). Platelets have a complex structure as might be expected from their multiple properties of adhesion to vascular surfaces, secretion, uptake of plasma constituents, aggregation with other platelets, and contraction. The structural features important in carrying out these functions include critical membrane proteins, intracellular storage granules, intracellular tubular and canalicular systems, and contractile and structural proteins. Figure 7.2 is a schematic diagram of a platelet.

The normal platelet count in humans is 150,000 to 400,000 per μL, with a mean of 250,000 per μL. The average life span of platelets in the circulation is 9 to 10 days. Generally the oldest platelets are removed from the vascular

system first, however, there appears to be a small random loss or consumption of platelets on the order of about 7,000/μL/day (4,5). This random disappearance is normally not noticeable; however, in severely thrombocytopenic individuals, it can be a large fraction of the total platelet mass and can make platelet transfusion support difficult. In rapid destruction states such as immune thrombocytopenia or disseminated intravascular coagulation (DIC), platelet counts can drop rapidly.

The process of forming an initial platelet hemostatic plug consists of three interactive steps: adhesion of platelets to the subendothelial tissue exposed by the wound, activation of adherent platelets, and activation and aggregation of other platelets to complete the plug. This process is mediated by a series of protein receptors on the platelet surface. Vascular injury exposes subendothelial collagen and other proteins to the flowing blood. Under conditions of high flow and shear, as occurs in the arterial system, platelets are moving across the surface of the injured vessel at relatively high speed. The first step in forming a platelet plug is to slow the platelets and bind them to the injured surface. This occurs through the protein complex GPIb-IX-V, the platelet von Willebrand factor receptor (6). Von Willebrand factor is a large multimeric protein that normally circulates in a globular form like a ball of string, with most of its binding sites covered. When collagen is exposed under conditions of high shear, as in the arterial system, von Willebrand factor binds to the collagen and unwinds in the flow exposing a large number of platelet binding sites (7–9). The higher the shear, or blood flow rate, the more the von Willebrand factor unwinds and stickier it gets. Platelets contact the multiple binding sites on von Willebrand factor, which slows the platelet as it moves across the sticky surface, eventually stopping it. In this way, von Willebrand factor can slow and bind platelets to a wound, even in rapidly flowing arterial blood. The von Willebrand factor receptor on platelets is always functional, but it only binds von Willebrand factor after von Willebrand factor binds to collagen and exposes its binding sites. Under conditions of rapid blood flow, von Willebrand factor-mediated adhesion is necessary for normal hemostasis. Patients with Bernard-Soulier syndrome, a moderate bleeding disorder characterized by a long bleeding time and a normal vWF level, lack one or several of the components of GPIb-IX-V (10). Their platelets do not adhere normally to exposed subendothelial tissue. Lack of, or dysfunctional von Willebrand factor, leads to von Willebrand disease. Three major subtypes have been described: type 1 von Willebrand disease is a mild to moderate autosomal dominant bleeding disorder due to low levels of normally functioning von Willebrand factor; type 2 von Willebrand disease has several subtypes all due to various abnormalities in the molecule that reduce or increase one or more of its functions; and type 3 is a severe, but rare autosomal recessive disease characterized by an almost complete lack of von Willebrand factor (11).

While binding of von Willebrand factor to its platelet receptor attaches the platelet to the wound and may activate the platelet to some extent (12), binding of the platelet to collagen through von Willebrand factor is insufficient to fully attach the platelet to the collagen or to fully activate the platelet. Once the platelet is slowed near the wound, lower affinity receptors on the platelet, GPIa-IIa (integrin $\alpha_2\beta_1$) and GPVI, bind the platelet directly to collagen which stimulates the initial activation of the platelet (13). Under conditions of low blood flow or shear, adhesion of platelets to subendothelial tissue may be mediated directly through the binding of the membrane receptor GPIa-IIa to collagen. However, binding of the platelet to collagen through von Willebrand factor is required for adhesion at higher shear rates. Lack of either the GPIa-IIa or GPVI receptors is associated with mild to moderate bleeding disorders (14,15).

Binding of ligands to platelet activation receptors leads to the activation of phospholipase C in the platelet membrane through G protein links (16). Phospholipase C in turn releases intracellular messengers that stimulate: (a) alpha and dense granule release, (b) shape and membrane changes in the platelet, and (c) conformational changes in the platelet fibrinogen receptor (GPIIb-IIIa = integrin $\alpha_{IIb}\beta_3$). Alpha granules are vesicles surrounded by lipid membranes that contain adhesive proteins (e.g., fibrinogen and von Willebrand factor), coagulation proteins (e.g., factor V), growth factors (e.g., platelet derived growth factor), and heparin binding proteins (e.g., platelet factor 4). (See Table 7.1.) When the platelet is activated, alpha-granules fuse with the outer lipid bilayer of the platelet releasing their contents and exposing proteins in the granule membrane, including the white cell binding protein P-selectin. Dense granules release ATP, calcium, and platelet activators including ADP and serotonin. Platelet activation also promotes thrombin generation and the formation of a fibrin clot. Platelet activation alters the phospholipid structure of the outer platelet membrane, exposing high affinity binding sites for coagulation factors Va and VIIIa. Factor V released from platelet alpha-granules binds to modified platelet surface where it is activated and serves as a high affinity factor X binding site. The surface-associated factor Va-factor Xa complex increases by several orders of magnitude the rate of thrombin generation over that of the proteins in solution (17). This is critical as thrombin is a powerful platelet activator itself.

Thrombin binds to and cleaves thrombin receptors on the surface of the platelet known as protease activated

TABLE 7.1
PLATELET GRANULE CONTENTS AND FUNCTIONS

Alpha Granule Proteins	Function
Von Willebrand factor	Binds platelets to collagen
Fibrinogen	Aggregates platelets, coagulation protein
Factor V	Accelerates coagulation
Platelet factor 4	Heparin binding protein, white cell chemotaxis
P-selectin	Binds white cells
Plasminogen activator inhibitor-1	Blocks plasminogen activation
Platelet derived growth factor	Stimulates cell proliferation, wound healing
Dense Granule Contents	**Function**
ADP	Platelet activator
Serotonin	Platelet activator
Calcium	Accelerates coagulation

receptors (PAR) (18). PAR proteins are unusual in that unlike other receptors, where binding of an external ligand activates the receptor (like collagen binding to the GPIa-IIa), thrombin binding itself does not activate PAR. The PAR molecule contains its own ligand in a cryptic form. Thrombin cleaves the PAR protein, releasing its own peptide ligand which then binds to and activates the PAR. There are several known PAR proteins on the platelet surface of which PAR-1 is the most important. A human PAR deficiency has not been described. Complete PAR-1 deficiency in knockout mice is fatal to approximately 50% of the mice during fetal development, but the others develop normally (19).

So far we have described factors external to the platelet, such as collagen and thrombin, which bind and activate the platelet. To recruit additional platelets and begin the process of platelet aggregation which completes the platelet plug, platelets release their own platelet activators including ADP and serotonin from dense granules and thromboxane produced by prostaglandin metabolism in the platelet. ADP released from dense granules activates other platelets in the vicinity of the forming clot by binding to platelet ADP receptors. Hereditary deficiency or mutation of these receptors leads to a mild bleeding syndrome (20). New medications, including clopidogrel and ticlopidine, have been developed to block the ADP receptor. These drugs are used to slow platelet activation and deposition on atherosclerotic arterial walls in patients with arterial thrombotic disease (21). Both drugs must be metabolized before becoming active; it is the metabolic product that blocks the ADP receptor. For this reason, the onset of drug action and the clearance of drug effect both take several days. Serotonin is another platelet activator that is released from dense granules when the platelet is activated. Serotonin or 5-hydroxytryptamine (5-HT) binds to the 5-HT-2 subtype of serotonin receptor. A similar receptor is present in the brain and is associated with depression. One class of medication used to treat depression, the selective serotonin uptake inhibitors, is associated with reduced serotonin reuptake in platelets and may lead to a mild increase in bleeding in some patients (22). A hereditary lack of alpha and/or dense granules in platelets is termed storage pool deficiency and is associated with an increased risk of bleeding. Patients without dense granules are unable to release ADP and serotonin to stimulate other platelets, these patients have a mild to moderate bleeding disorder (23).

In addition to releasing factors from granules that stimulate other platelets, activated platelets synthesize and secrete a powerful platelet activator, the eicosanoid thromboxane. Thromboxane A_2 (TXA_2) generated by platelets induces platelet aggregation and vasoconstriction. TXA_2 is formed from arachidonic acid released from membrane phospholipids by phospholipase A_2. Using arachidonic acid, the enzyme cyclooxygenase begins a synthetic sequence leading to TXA_2 production in platelets. This same pathway is used to produce prostacyclin (PGI_2) in endothelial cells. PGI_2 is a strong platelet inhibitor. The secretion of PGI_2 by endothelial cells also accounts for aspirin's antiplatelet effects. Aspirin irreversibly acetylates cyclooxygenase that is present in both platelets and endothelium (24). However, the effects of aspirin on platelets differ from its effects on endothelial cells. The reason is that cyclooxygenase is made constitutively in endothelial cells, but circulating platelets do not make it. All cyclooxygenase in platelets is synthesized in the megakaryocytes before the platelets are released. After low dose aspirin exposure, endothelial cells soon recover the ability to make PGI_2, but only newly

released platelets make TXA_2. Therefore, the net effect of low dose aspirin is that endothelium continues to make the platelet inhibitor PGI_2, but the thromboxane activation pathway in platelets is blocked. Another class of medications that inhibit cycloxygenase and platelet activation are the non-steroidal anti-inflammatory drugs (NSAID) typified by ibuprofen. Unlike aspirin, which is an irreversible cyclooxygenase inhibitor, NSAIDs are reversible competitive inhibitors, as the drug clears from the blood the inhibition effect is eliminated as well. There are two forms of cycloxygenase (COX-1 and COX-2). Platelets contain only the COX-1 form of the enzyme. New selective COX-2 inhibitors (celexocib and refecoxib) have no antiplatelet activity.

One of the most important effects of platelet activation is the resulting conformation change and activation of GPIIb-IIIa, the platelet fibrinogen receptor. GPIIb-IIIa is the most abundant glycoprotein on the platelet surface, but in the resting platelet GPIIb-IIIa is inactive, unable to bind fibrinogen. When the platelet is activated, GPIIb-IIIa undergoes a conformational change that exposes its fibrinogen binding site. A number of proteins, including fibrinogen, vitronectin, fibronectin, and von Willebrand factor, bind to activated GPIIb-IIIa. The most important plasma protein for platelet aggregation is fibrinogen, which has the highest plasma concentration and multiple GPIIb-IIIa binding sites per fibrinogen molecule. Binding of fibrinogen molecules to activated GPIIb-IIIa receptors pulls platelets together, aggregating them, increasing the platelet mass at the site of the wound, and ultimately leading to the initial hemostatic platelet plug. New medications including a humanized monoclonal antibody (abciximab) and short peptides (tirofiban) have recently been developed that bind to and block the GPIIb-IIIa site on platelets, slowing platelet aggregation. These medications are used to help prevent rapid reocclusion in coronary arteries after percutaneous angioplasty by slowing platelet aggregation at the site of angioplasty procedure (25). Lack of GPIIb-IIIa causes the most severe congenital disease of platelet dysfunction, Glanzmann's thrombasthenia (26). People with thrombasthenia have normal platelet counts but a moderately severe bleeding disorder commonly manifested by prolonged life-threatening bleeding in childhood or early adolescence. The platelets in thrombasthenia have no ability to form a hemostatic plug. The bleeding time is infinite and platelet aggregation is zero.

Activation of platelets causes a change in their shape from small discs to elongated shapes having long protrusions (pseudopods) which increases the interaction with other platelets and covers the wounded surface more effectively. This shape change and the later contraction that consolidates the aggregated platelets, involves platelet actin polymerization, which is also triggered during platelet activation. Another important platelet receptor exposed during platelet activation is P-selectin, which mediates the binding of monocytes and neutrophils to the platelets. Activated white cells express tissue factor on their surface and may transfer tissue factor to the platelet membrane, increasing coagulation activation on the platelet surface (27).

In the early days of hemostatic research, platelet function was analyzed using the bleeding time, essentially a measure of how fast initial hemostatic plug formation occurred in response to a controlled cutaneous wound. This assay was instrumental in analyzing the mechanism behind von Willebrand disease and other platelet function abnormalities. While useful in research, the bleeding time is not useful for screening of platelet function prior to surgery and has been supplanted for evaluation of most platelet function abnormalities by more specific tests (28). Reviews have shown that bleeding times do not predict perioperative risks of bleeding (29–32). Many hospitals no longer perform bleeding times clinically.

It is possible to detect platelet activation occurring in vivo using platelet activation markers (33–35). When platelets are activated they release platelet specific proteins like platelet factor 4 and beta-thromboglobulin. The level of these proteins in plasma is an indication of the amount of platelet activation that is occurring. Another method of evaluating platelet activation is to use flow cytometry to measure changes in proteins on the platelet surface. Platelet activation increases the number of P-selectin receptors and activated GPIIb-IIIa receptors on the platelet and increases the exposure of platelet anionic phospholipids.

Platelets are metabolically active cells. They have abundant glycogen stores to maintain ATP production. In storage of platelet concentrates, care must be taken to agitate the suspensions and provide for adequate O_2 and CO_2 exchange through the plastic bags or platelet function declines. Upon stimulation by aggregating agents, such as collagen or thrombin, there is a burst of oxidative metabolic activity. Although formation of the platelet plug is the critical first step of hemostasis, the platelet plug is temporary. Platelets require continued ATP generation to maintain both their contractility and the hemostatic integrity of the platelet plug. If a fibrin clot does not form at the site of the wound, the platelet plug will fall apart within about 24 to 48 hours, due in large part to the depletion of ATP in the platelet. Once it breaks down, it usually does not reform. An illustration of this is the well-known pattern of delayed bleeding in hemophiliacs or individuals with other coagulation protein deficiencies. In hemophilia, platelet function is essentially normal; small or moderately sized wounds usually stop bleeding in a few minutes, as they would in someone without hemophilia.

When the platelet plug disperses in 24 to 48 hours, however, the wound begins to bleed, and prolonged oozing is the rule, because the clotting factor deficiency blocks the formation of a renewable fibrin clot.

Increased platelet counts (thrombocytosis) can occur as a reaction to a transient reduction in platelets that stimulates new platelet formation in the bone marrow (reactive thrombocytosis), in response to infection, inflammation, drugs or anemia, or as part of a myeloproliferative syndrome analogous to chronic myelogenous leukemia (essential thrombocythemia) (36). Decreased platelet counts can occur due to decreased production in the bone marrow (e.g., drug reactions, neoplastic bone marrow replacement), increased destruction from immune causes or blood loss, or increased consumption as occurs in disseminated intravascular coagulation (DIC).

COAGULATION SYSTEM

After formation of the platelet plug, the next stage is clot stabilization by the coagulation system. As discussed in the section above, while platelets are fast at initially plugging the wound, platelets require continuous metabolic activity to maintain clot stability, preventing the platelets from maintaining the hemostatic plug on their own for more than about 24 to 48 hours. Furthermore, the platelet plug is limited in strength, so that mechanical stress at the site of the wound can break it down even faster. Stabilization and strengthening of the clot is the job of the coagulation system. To begin our discussion of coagulation, we must first introduce the players: (a) tissue factor that initiates coagulation, (b) factors VII, IX, X, XI and prothrombin-proteolytic enzymes that amplify the tissue factor trigger, (c) factors V and VIII that accelerate the production of the proteolytic enzymes, (d) fibrinogen that forms the polymeric meshwork that strengthens the clot, and (e) factor XIII that cross-links the fibrin resulting in a final stable hemostatic plug (17).

Coagulation is initiated by the exposure of trace amounts of tissue factor in subendothelial tissues and possibly through the delivery of tissue factor to the wound by white blood cells (27). Tissue factor is a membrane-bound protein present on the surface of fibroblasts, tissue stroma, and other cells associated with blood vessels throughout the body (37). During fetal development, tissue factor plays a critical role in normal blood vessel development; lack of tissue factor in knockout mice is usually fatal during fetal development (38). Much of the tissue factor present in cells is not exposed on the surface, instead it is encapsulated in outer membrane invaginations called caveolae (39). When the cell is activated, these membrane pockets open up exposing the enclosed membrane-bound tissue factor. While tissue factor is the trigger that starts coagulation activation, the amplification occurs through a series of similar proteolytic enzymes. The vitamin K-dependent serine proteases, prothrombin (factor II), factor VII, factor IX, and factor X, are all made in the liver as inactive zymogen proteins that must be proteolytically cleaved to form the active enzymes thrombin (factor IIa) and factors VIIa, IXa and Xa (40). They have similar structures including an active serine protease domain and calcium-binding domains containing gamma-carboxyglutamic acid (Gla) residues that result from posttranslational carboxylation of the newly synthesized proteins. This is the step that requires vitamin K. Historically, these four proteins have been grouped together because of the common requirement for vitamin K (and conversely, the production of inactive forms by the anticoagulant warfarin, a vitamin K antagonist). These proteins have other similarities as well. Factors VII, IX, and X share two epidermal growth factorlike domains, whereas in the same region of the molecule, prothrombin has two kringle domains. Two regulatory proteins, protein C and protein S are also vitamin K dependent proteins. Both have calcium-binding and epidermal growth factor domains. Protein C has a serine protease domain, while protein S, which acts as a cofactor for protein C, is the only nonprotease in the group.

Coagulation factors V and VIII are similar high molecular weight cofactors that aid in the assembly of enzyme complexes on the platelet surface that accelerates coagulation activation (41,42). Both have multiple A and C domains that show a high degree of homology. Factor V is made in the liver. The cell of origin for factor VIII is unknown but may include hepatocytes or the reticuloendothelial system. Both proteins circulate in an inactive form that is converted to the active cofactor through proteolytic cleavage by either factor Xa or thrombin. Factor V is found in platelet alpha granules and on platelet membranes in addition to circulating in plasma. Factor VIII circulates bound to von Willebrand factor. After activation, both factors Va and VIIIa bind to the platelet surface.

Fibrinogen is a large protein produced in the liver that consists of three pairs of different polypeptide chains held together by disulfide bonds (43). Each fibrinogen molecule has three large globular regions separated by long, thin helical peptide strands. The globular regions on each end are designated the D-domains and participate in D-dimer formation. Fibrinogen is converted into fibrin by the enzyme thrombin which cleaves four peptide bonds on fibrinogen releasing fibrinopeptides A and B and exposing polymerization sites that then allow the overlapping polymerization of fibrin monomers into a fibrin clot meshwork. Coagulation factors XI and XIII are the final

members of the coagulation system; they bear little resemblance to any of the other proteins. Although it is a serine protease, factor XI is not homologous with the vitamin K dependent factors, it shares with them only the trypsinlike protease domain (44). Factor XIII is a transglutaminase that forms covalent cross-links between fibrin molecules strengthening the clot and making it more resistant to fibrinolysis (45). In addition, factor XIII cross-links the fibrinolytic inhibitor α_2-antiplasmin to fibrin, further slowing lysis. Factor XIII is present in platelets, monocytes, and macrophages.

Activation of Coagulation

The purpose of the coagulation system is to amplify an initial trigger (exposure of tissue factor) into a rapid process for producing fibrin to stabilize the forming hemostatic clot, while at the same time limiting the spread of the clotting process to the site of injury to avoid widespread thrombosis. Figure 7.3 shows a simplified version of the coagulation system. The critical step in coagulation activation is the formation of the active enzyme thrombin (46). Thrombin plays many roles in hemostasis including platelet activation, conversion of fibrinogen to fibrin, and the activation of coagulation factors V, VIII, XI, XIII, and protein C. Recent studies have elucidated how thrombin generation is regulated under ideal conditions (47). Thrombin generation occurs in two phases, termed the initiation phase and propagation phase. The initiation phase begins with the exposure of tissue factor and early platelet activation. Under normal conditions approximately 1% of factor VII circulates in an active form (VIIa) (48). Factor VIIa is slow at activating factor IX or X unless it is bound to tissue factor. Therefore the tiny amount of circulating factor VIIa does not activate coagulation in the absence of tissue factor and activated platelets at the site of a wound. When a vascular injury occurs and tissue factor is exposed on cell surfaces, both unactivated factor VII and the small amount of circulating factor VIIa binds to the exposed tissue factor forming complexes that begin the coagulation process (Fig. 7.4) (49). When unactivated factor VII binds to tissue factor, it changes the conformation of factor VII enhancing its activation by VIIa, IXa, and Xa. Tissue factor also acts as a cofactor to factor VIIa, this complex activates three different proteins: a) more factor VII into VIIa, b) factor IX to IXa and c) factor X to Xa.

Each time VIIa-tissue factor complex activates a factor IX, the IXa can go on to activate many factor X molecules. This is the concept of the amplification process. In contrast, when tissue factor-VIIa complex directly activates factor X, it is making Xa one at a time and little amplification occurs. During the initiation phase, early on in the coagulation activation process before cofactor VIII is activated, factor IXa by itself activates a small amount of factor X to Xa. Likewise, prior to cofactor V activation, factor Xa by itself converts a small amount of prothrombin into thrombin. Initial formation of thrombin is the critical rate-limiting step in accelerating coagulation. While there are many different factors that thrombin activates, during the initiation phase of coagulation the most important role thrombin plays is the activation of platelets and the activation of the cofactors VIII to VIIIa and V to Va (50,51). As described above, activated platelets expose binding sites for coagulation factors on their surface. Once coagulation cofactors VIII and V are activated by thrombin, they bind to these

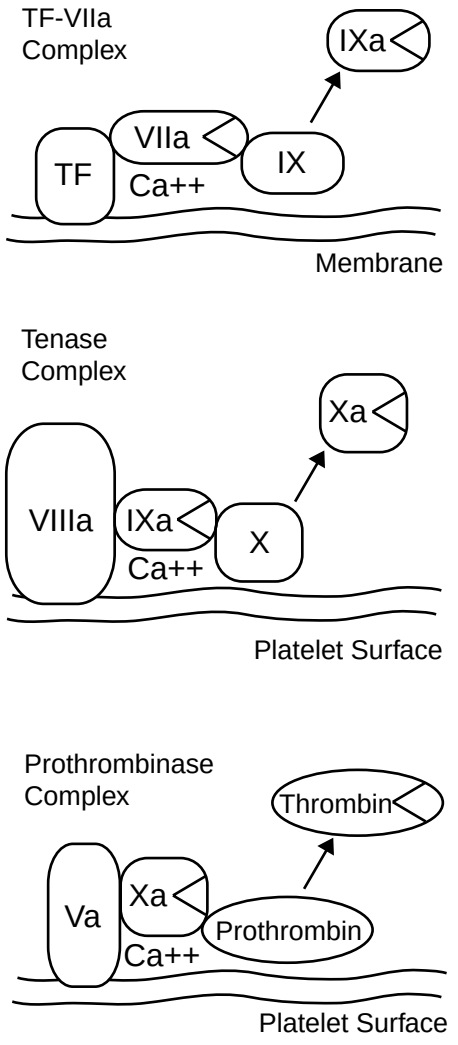

Figure 7.4 Diagrams showing the three major enzyme complexes that form on the platelet surface as part of the coagulation amplification process. Note the similarity in the structure of the tissue factor-VIIa, tenase, and prothrombinase complexes. Each consists of a cofactor (tissue factor, VIIIa, and Va) bound to the platelet surface along with a vitamin K dependent protease (VIIa, IXa, and Xa) that binds to the platelet through calcium-dependent domains and a proenzyme to be activated (IX, X, and prothrombin).

sites on the platelet surface (see Fig. 7.4). Factor IXa binds with factor VIIIa on the platelet surface forming the "tenase" complex that activates factor X to Xa hundreds of times faster than factor IXa does alone. Likewise, factor Xa binds with factor Va to the platelet surface forming the "prothrombinase" complex that activates prothrombin to thrombin hundreds of times faster than factor Xa does alone. All three cofactors, tissue factor, Va and VIIIa, function to aid assembly of the catalytic complex on the platelet phospholipid surface and to promote the specific binding of the proper substrate to the complex. Figure 7.4 shows the remarkable similarity to the VIIa-tissue factor, IXa-VIIIa and Xa-V complexes, all designed to accelerate thrombin and fibrin formation near the platelet, the recurring paradigm of clotting reactions. Once sufficient platelet activation, VIIIa and Va formation occurs, the second or propagation phase of coagulation occurs. During this phase, thrombin generation rapidly increases. As the level of thrombin rises, it in turn converts more and more fibrinogen into the sticky protein fibrin, which polymerizes enveloping the platelet plug and trapping additional platelets, red cells, and white cells stabilizing and strengthening the clot. A small amount of fibrin is made during the initiation phase, but the major fibrin formation is during the second or propagation phase as thrombin generation rapidly increases.

The rate of thrombin generation during the initiation phase is dependent on the amount of tissue factor exposed and the number of platelets initially activated (52). In contrast, once the propagation phase of rapid thrombin generation begins it is essentially tissue factor concentration independent, clotting usually proceeds to completion. Part of what appears to determine normal versus inadequate hemostasis is whether the coagulation system is capable of transitioning from the initiation to the propagation phase. During the propagation phase thrombin increases its activation of factor XI to XIa, which helps sustain factor IX activation as the tissue factor is covered by the growing clot, and activates factor XIII to XIIIa, which cross-links fibrin molecules in the clot. These cross-links make the clot stronger and more resistant to lysis by the fibrinolytic system. As the clot completely covers the wound site and no more collagen or tissue factor are exposed, coagulation and platelet activation slow down. There is a steady slow rate of coagulation activation and fibrin formation offset by continuous slow lysis of the clot which controls the size of the clot until the wound is covered by endothelium or epithelium as part of wound healing.

The rates of thrombin and fibrin generation occurring in vivo can be detected using thrombin activation markers. When prothrombin is converted to thrombin, it releases an activation peptide F1.2 (53,54). Active thrombin remains in the blood only a short time before it is inhibited by antithrombin forming thrombin–antithrombin complex (55). The concentration of F1.2 and thrombin–antithrombin complex are measures of the rate of thrombin generation in blood (56). When thrombin converts fibrinogen to fibrin it releases fibrinopeptides A (FPA) and B (FPB) into plasma. The concentration of FPA can be used to estimate the rate of fibrin generation (56,57).

Coagulation Factor Deficiencies

No human with tissue factor deficiency has been described, and based on knockout mice models, tissue factor deficiency does not appear to be compatible with normal fetal vascular development (38). Hereditary factor VII deficiency is a rare autosomal recessive disorder and has been reported to have variable bleeding associated with it, but in general severe deficiency (<1%) is often associated with severe bleeding, while patients with factor VII levels above 5% generally have only moderate to mild bleeding (58). Only a small amount of factor VII appears to be needed to start the coagulation process. As described above, once the propagation phase of coagulation activation is reached and rapid thrombin generation has started, tissue factor and factor VII levels are relatively unimportant. Deficiencies of factors VIII and IX (hemophilia A and B) are more common with approximately 80% due to factor VIII deficiency and 20% due to factor IX deficiency (59). Hemophilia A and B have similar clinical features: sex-linked recessive disorders with the most severe bleeding problems of any coagulation factor deficiencies. Severe bleeding occurs in virtually all patients with less than 1% factor VIII or IX, moderate bleeding with levels between 1% and 10%. Levels of 30% or more are required for near normal hemostasis after major surgery or trauma. Factor X deficiency is a rare autosomal recessive condition, similar in severity to hemophilia A and B, with levels of 15% to 20% required to prevent bleeding after surgery or trauma (60). The severe bleeding associated with factor VIII, IX, and X deficiencies reflect the importance of these reactions in the coagulation amplification process between tissue factor and thrombin generation in all subjects. Severe factor V deficiency is often associated with bleeding, but it is complicated by the fact that factor V is present in platelets as well as plasma and that both may need to be deficient for bleeding to occur (61). Prothrombin deficiency is also not a severe bleeding risk unless the lack of the protein is nearly complete (62). The reason for this is different; it probably has to do with the large molar excess of prothrombin over the minimum needed and with the explosive generation of thrombin. Under physiological conditions, the local conversion near platelets of only 10% to 15% of the prothrombin in plasma provides more than enough thrombin for normal fibrinogen clotting. Hemophilia C due to

factor XI deficiency is a mild to moderate bleeding disorder that shows poor correlation between standard factor XI activity levels and bleeding severity (44).

In addition to deficiencies, some patients develop antibodies to the coagulation factors which reduce the activity of the factor even though it is present in plasma (63). This is most common in severe hemophilia A (less than 1% factor VIII) where the transfused factor VIII is seen as a foreign protein and antibodies are made against it. Antibodies can spontaneously form against factor VIII and other coagulation factors in a variety of patients including the elderly, post-partum, and autoimmune diseases. Factor inhibitors can be difficult to treat as the antibody inhibits any new factor that is infused. One new therapy that has been developed to bypass factor VIII or IX inhibitors in particular is human recombinant activated factor VII (rVIIa) (64). Large doses of rVIIa, equivalent of 100 times the normal circulating level of VIIa, are effective at stimulating hemostasis in bleeding patients with factor VIII inhibitors, presumably by activating factor X directly through tissue factor dependent and independent mechanisms (64,65).

The normal fibrinogen concentration, 2.5 mg per mL, is substantially in excess of the minimum needed for normal clot formation under most conditions. Usually, normal surgical hemostasis can be expected if the plasma fibrinogen is greater than 1.0 mg per mL. Fibrin polymerization can be inhibited in a number of ways. Certain abnormal fibrinogens polymerize slowly, either because of delayed release of fibrinopeptides or because of an inherently slower rate of fibrin monomer polymerization (66). The most common acquired inhibitors of fibrin monomer polymerization are high molecular weight fibrin degradation products that result from partial cleavage of fibrin by the fibrinolytic protease plasmin. A deficiency of factor XIII, although not affecting the formation of the fibrin clot, causes a rare bleeding disorder that can be moderately severe if the deficiency is nearly complete (67). Only small amounts of factor XIII, a few percent of normal, are required for normal hemostasis. Higher levels of factor XIII may be necessary for normal wound healing (68). The most common acquired deficiency of coagulation factors is due to vitamin K deficiency or warfarin therapy. Both produce a reduction in the activity of the vitamin K dependent proteins, factors VII, IX, X, prothrombin, protein C, and protein S.

Intrinsic and Extrinsic Pathways

For many years the coagulation cascade was described as having two arms, the intrinsic and extrinsic pathways. In one, the blood contained all the necessary factors (the blood or intrinsic pathway); in the other, a factor or factors present in tissue were involved (the extrinsic or tissue pathway). It is now known that only a single pathway exists in vivo, as shown in Figure 7.3. The basis of the two pathway model was the early assays used to assess the coagulation system, the prothrombin time or PT, and the activated partial thromboplastin time or aPTT. In 1935, Quick developed the prothrombin time, which consisted of adding a large amount of exogenous tissue factor and phospholipid along with calcium to citrated plasma (69). Quick demonstrated that the prothrombin time was normal in hemophilia, indicating the abnormality lay outside the direct tissue factor pathway. So much tissue factor and phospholipid were added during the PT assay that clotting could be induced by direct VIIa-tissue factor activation of factor X, factors VIII and IX were not needed. Thus, the PT was sensitive to deficiencies of factors VII, X, V, prothrombin, and fibrinogen.

In the aPTT assay, coagulation is activated in citrated plasma using glass or another negatively charged surface. When plasma is exposed to glass, it activates the contact or kallikrein/kinin system, resulting in the formation of activated factor XII. In the presence of calcium and phospholipid, factor XIIa activates factor XI to XIa, which in turn activates factor IX to IXa starting the coagulation cascade. Use of a contact system activator like ground glass bypasses the tissue factor activation that normally occurs to start coagulation. The aPTT is sensitive to deficiencies of factor VIII, IX, and XI, and to a lesser extent X, V, prothrombin, and fibrinogen. The aPTT is also sensitive to deficiencies of the contact system proteins: factor XII, prekallikrein, and high molecular weight kininogen. In vivo ground glass is not present as a coagulation activator, and even severe deficiencies of the contact system proteins including factor XII are not associated with bleeding. So, while activation of the contact system works in the aPTT assay to make it sensitive to factors VIII, IX, and XI, it plays little role in vivo in normal coagulation activation. In vivo tissue factor initiates essentially all coagulation and factors VIII and IX are required to accelerate clotting, thus only a single pathway exists in vivo even though different pathways are used in the PT and aPTT assays. Once thrombin is generated it activates factor XI which helps to maintain factor IX activation (Fig. 7.3).

REGULATION OF HEMOSTASIS

In the absence of vascular injury, hemostatic activation must be blocked to prevent pathologic thrombus formation and vascular occlusion. The front line in the prevention of pathologic thrombosis is the vascular endothelial cell, which lines the blood vessels. Healthy, normal endothelium are nonthrombogenic. It has long been

known that both platelets and coagulation are activated by vascular damage that exposes blood to contact with the subendothelium. For this reason, one important way vascular endothelium provide a barrier to hemostatic activation is simply the prevention of blood contacting proteins in subendothelial tissue. Disorders that cause endothelial damage, including certain bacterial, viral, or rickettsial infections and primary vascular disorders, may be associated with local microthrombus formation. In addition to being a passive barrier, endothelium secrete factors and express proteins on their surface that block platelet and coagulation activation and stimulate fibrinolysis (Fig. 7.5). Endothelial cells are not always anticoagulant cells, in response to injury, inflammation, infection, and other stimuli, vascular endothelial cells can become activated changing into procoagulant cells that stimulate thrombus formation. Normal versus activated endothelial cells play opposite roles in regulating hemostasis.

Normal endothelial cells block platelet activation in several ways. The main platelet inhibitors, prostacyclin (PGI_2) and nitric oxide, prevent the initial steps of hemostasis: platelet adhesion and aggregation. PGI_2 and nitric oxide are synthesized by endothelial cells; both relax smooth muscle on the adventitial side of vessels and both are potent, although labile, inhibitors of platelet aggregation. The arachidonic acid pathway, by generating both activators and inhibitors of platelets, is a means of regulating platelet function (70). Prostacyclin is rapidly degraded in plasma and thus has mainly a local effect at the endothelial surface. The main function of nitric oxide appears to be to regulate vascular tone, but it also inhibits platelet aggregation and adhesion by raising platelet cGMP. When endothelial cells are activated, they stop secreting prostacyclin and nitric oxide and instead begin producing the powerful platelet activator thromboxane. When the injury or activation stimulus is over, the endothelial cell reverts back to its antithrombotic mode and again produces prostacyclin and nitric oxide.

Normal endothelial cells have at least three major systems for inhibiting coagulation activation (Fig. 7.6). The first inhibitor of the coagulation system is tissue factor pathway inhibitor (TFPI), a kunitz-type inhibitor produced by endothelial cells. TFPI by itself is inactive. To become active, TFPI must first bind to factor Xa. This TFPI-Xa complex then binds to and inhibits the VIIa-tissue factor complex stopping coagulation activation at its source. Thus,

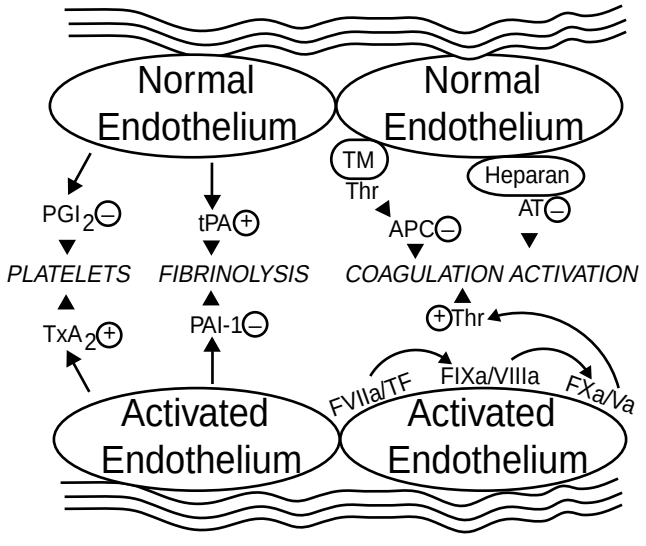

Figure 7.5 Diagram of normal and activated endothelial cell surfaces showing some of the reactions that stimulate (+) or inhibit (-) platelets, fibrinolysis, and coagulation activation. Normal endothelial cells are anticoagulant cells that actively block clot formation. Activation of endothelial cells due to injury, infection, inflammation, or other causes results in a procoagulant cell. PGI_2, prostacyclin; TxA_2, thromboxane; tPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor 1; TM, thrombomodulin; Thr, thrombin; APC, activated protein C; and AT, antithrombin.

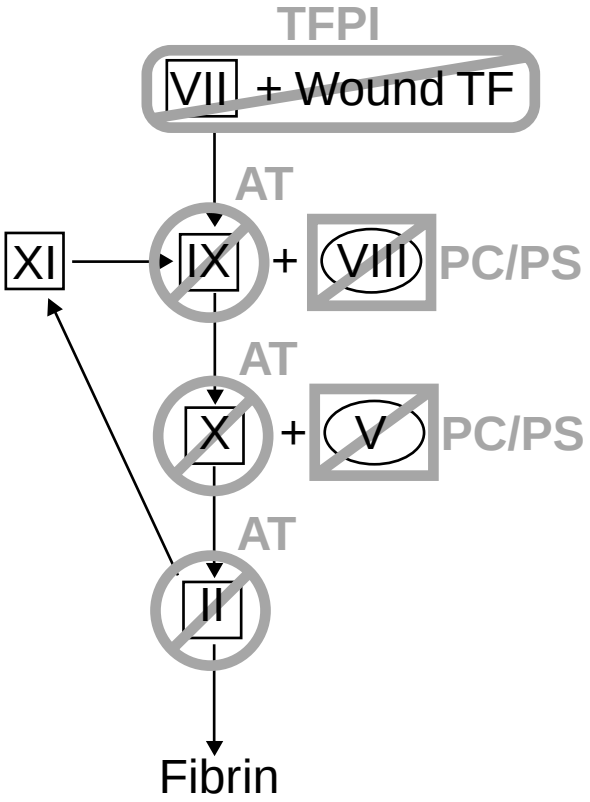

Figure 7.6 Diagram showing the three main regulatory systems that block coagulation activation. Tissue factor pathway inhibitor (TFPI) binds first to activated factor X, this complex then binds to and inhibits the VIIa-tissue factor complex. Antithrombin (AT) accelerated by either endothelial heparan sulfate proteglycans or heparin, binds to and inhibits the active serine proteases thrombin, IXa, Xa, and XIa. Activated protein C (APC) in conjunction with protein S (PS), destroys the cofactors Va and VIIIa by proteolytic cleavage.

TFPI only works as an inhibitor after significant levels of activated factor X are formed by coagulation activation, at which time it begins shutting down coagulation activation by tissue factor. Based on knockout mouse models, complete deficiency of TFPI is lethal during fetal development. Mice with heterozygous deficiencies do not show thrombotic abnormalities (71). A definite relationship between low levels or mutations in TFPI in humans and thrombosis has yet to be established.

The next step in the regulation of coagulation activation is the antithrombin-heparan system. Antithrombin binds to and inactivates thrombin, factor IXa, Xa, and XIa. In the absence of heparin or cell-associated heparan sulfates, the rate of thrombin inhibition by antithrombin is slow. Endothelial cells express heparan sulfate proteoglycans on their surface. These molecules bind antithrombin and increase the rate of thrombin inhibition by antithrombin several 100-fold. In essence then, normal endothelium are coated with a layer of antithrombin bound to endothelial heparan sulfate which rapidly neutralizes any free thrombin, IXa, Xa, or XIa in the circulation, thus blocking thrombin and fibrin generation from occurring away from the site of the wound. Thrombin and factor Xa bound to the platelet surface or to fibrin are protected from endothelial-bound antithrombin. When heparin is infused, it accelerates thrombin and factor Xa inhibition by antithrombin in the same way as endothelial heparan sulfate, but with the added advantage that heparin circulates freely and thus can accelerate the inhibition of clot bound thrombin and factor Xa as well as free circulating forms. Thus, heparin can slow thrombus formation in hyperthrombotic states, but also leads to an increased risk of bleeding due to neutralization of clot bound thrombin and factor Xa at wound sites. Standard unfractionated heparin accelerates the destruction by antithrombin of both thrombin and factor Xa. Low molecular weight heparin and new synthetic pentasaccharide medications like fondaparinux primarily accelerate the destruction of factor Xa by antithrombin (72). Therefore, low molecular weight heparin activity is measured using an anti-Xa activity assay.

Platelets express the heparin binding protein PF4 on their surface. Some patients develop antibodies to the heparin-PF4 complex. Antibodies form 7 to 10 days after starting heparin resulting in platelet activation, thrombocytopenia, and arterial and venous thrombosis (heparin-induced thrombocytopenia syndrome) (73). In these situations heparin cannot be used, instead a new class of antithrombotic agents are given, the direct thrombin inhibitors. These medications include recombinant versions of hirudin, a thrombin-inhibiting molecule produced in leeches, and small molecule inhibitors of thrombin such as argatroban and the short peptide bivalirudin (74).

Once thrombin is generated, yet another inhibitory mechanism comes into play. Normal endothelial cells express the protein thrombomodulin on their surface, which binds thrombin. The effects of this are twofold. First, thrombin is removed from the circulation, again minimizing the chance of generalized clotting of fibrinogen. Second, binding to thrombomodulin causes a conformational change in thrombin, which blocks thrombin's ability to activate platelets, fibrinogen, and factors V and VIII, while at the same time increasing thrombin's ability to activate protein C. Thus, free thrombin reaching the endothelial surface is either inhibited by antithrombin or binds to thrombomodulin and activates the protein C system. Activated protein C in conjunction with its cofactor protein S destroys the coagulation cofactors Va and VIIIa, slowing coagulation activation by limiting the activation of factor X and prothrombin. A recombinant version of activated protein C (drotrecogin alfa) has been developed to block excessive coagulation activation that occurs in sepsis associated disseminated intravascular coagulation (75). Activation of endothelium changes the cells from an anticoagulant to a procoagulant cell. Production of TFPI and thrombomodulin are decreased and the activated endothelial cells expose binding sites for activated coagulation factors resulting in thrombin and fibrin formation near the endothelial surface.

Homozygous deficiencies of antithrombin, protein C, or protein S are rare and are associated with a severe thrombotic syndrome soon after birth termed neonatal purpura fulminans (76). Heterozygous deficiency of these proteins occurs in about 1:1000 people and results in levels about 50% of normal leading to an increased risk of venous thromboembolism (77). Another common risk factor for venous thrombosis is a single nucleotide mutation in the factor V gene (factor V Leiden) that makes factor V resistant to the proteolytic effect of activated protein C. The factor V Leiden mutation has a frequency of about 5% in North American and European populations accounting for up to 30% of the patients with recurrent familial venous thrombosis. Recent studies have found that persistent elevations of coagulation factor levels are also associated with an increased risk of venous thrombosis. The best understood of these abnormalities is a single nucleotide mutation in the prothrombin gene that is associated with elevated prothrombin levels (78). Persistent elevations of factor VIII, IX, and XI associated with increased venous thrombotic risk have also been described (79).

FIBRINOLYSIS

The regulatory systems described above function to block platelet and coagulation activation away from the site of

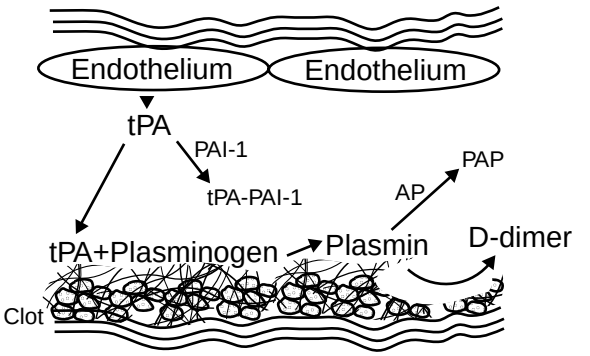

Figure 7.7 Diagram showing important aspects of the fibrinolytic system. Tissue plasminogen activator (tPA) is released from endothelial cells lining the vessel wall. tPA binds along with plasminogen to fibrin clots where it converts the plasminogen into plasmin, which in turn dissolves or lyses the clot releasing fibrin degradation fragments including D-dimer. tPA activity in plasma is controlled by plasminogen activator inhibitor 1 (PAI-1) which binds to and inhibits tPA forming inactive tPA-PAI-1 complexes. Plasmin activity in plasma is controlled by antiplasmin (AP) which binds to and inhibits plasmin forming inactive plasmin–antiplasmin complexes (PAP).

the wound. In contrast, the fibrinolytic system regulates the size of the thrombus itself and prevents widespread fibrin accumulation in the vascular system (80). Fibrinolysis is initiated by the release of tissue plasminogen activator (tPA) from normal endothelial cells (Fig. 7.7). tPA is a serine protease that binds along with plasminogen to fibrin, where it converts plasminogen into the active enzyme plasmin. In turn, plasmin cleaves fibrin forming a series of degradation fragments including D-dimer. tPA is a slow activator of plasminogen in the absence of fibrin. When fibrin is present, it accelerates the activation of plasminogen approximately 1000-fold. As fibrin is degraded its ability to accelerate plasminogen activation is lost. Thus, fibrinolysis is normally a self-regulating system. Fibrin in the vascular system leads to plasminogen activation by tPA. As fibrin is removed or covered over during wound healing, plasmin generation falls. Urokinase plasminogen activator (uPA) is second plasminogen activator made by a variety of extravascular cells where it controls plasmin generation associated with tissue remodeling and other processes. uPA has only a minor role in the regulation of intravascular thrombus formation.

The amount of fibrin in the vascular system is a dynamic function of the rate of fibrin formation by the coagulation system versus the rate of fibrin degradation by the fibrinolytic system. The level of D-dimer in the blood is a measure of the amount of intravascular fibrin that is present. Low D-dimer levels indicate little fibrin is present anywhere in the vascular system, whereas high D-dimer indicates fibrin formation and lysis are occurring. Increased plasmin generation is associated with increased fibrin removal and bleeding, reduced plasmin activity is associated with intravascular fibrin accumulation and thrombosis. The level of tPA activity in blood is one of the most important regulators of plasmin generation. The activity of tPA in plasma is regulated by an inhibitor, plasminogen activator inhibitor 1 (PAI-1), which binds to and inactivates tPA forming tPA/PAI-1 complex. While tPA free in plasma is rapidly inhibited by PAI-1, inhibition of fibrin-bound tPA by PAI-1 is much slower. Thus, the PAI-1 system is designed to limit activation of plasminogen by tPA to fibrin clots while protecting against random activation of plasminogen in solution. The activity of plasmin is regulated by an inhibitor, antiplasmin, which binds to and inactivates plasmin forming plasmin-antiplasmin complex. Like tPA, plasmin bound to fibrin is inhibited by antiplasmin about twenty times slower than free plasmin. The concentration of active tPA in blood is a function of the rate of tPA secretion from normal endothelial cells, the concentration of its inhibitor PAI-1, and the rate of clearance of tPA by the liver. tPA secretion from endothelial cells can be increased manyfold in minutes, rapidly accelerating fibrinolysis (81,82). An example of this is seen during cardiopulmonary bypass, which stimulates a fivefold increase in tPA secretion within minutes of starting bypass (83). Increased tPA levels during cardiopulmonary bypass along with increased fibrin formation in the bypass circuit leads to increased plasmin generation and increased fibrin degradation which is associated with an increased risk of bleeding postoperatively. This has led to development of medications to slow fibrinolysis including aprotinin, an inhibitor of plasmin and other proteases, and lysine analogues like tranexamic acid and epsilon-amino-caproic acid that reduce binding of plasmin to fibrin. Plasminogen activators have been developed for the treatment of arterial and venous thromboembolic disease. A recombinant form of tPA is commonly used to treat myocardial infarction. Large doses of tPA or other plasminogen activators are infused to activate plasminogen and lyse the coronary thrombus (84). tPA has also been used to treat thromboembolic stroke, but the treatment is risky as the benefit of thrombolysis is often outweighed by the risk of intracranial hemorrhage (85).

Another cause of increased active tPA is the deficiency of PAI-1 (86). Complete PAI-1 deficiency leads to a mild delayed bleeding disorder characterized by postoperative wound hematomas. Bleeding is also associated with deficiencies of antiplasmin. Heterozygous antiplasmin deficiency results in levels about 50% of normal and is associated with a mild delayed bleeding risk similar to complete PAI-1 deficiency. Homozygous antiplasmin deficiency is rare, but is associated with a more severe bleeding risk. A third cause of increased active tPA is reduced clearance.

Normally the liver clears about 50% of the tPA from blood with each pass, giving tPA a half-life of only 3 to 5 minutes (87,88). Patients with advanced cirrhosis have reduced clearance of tPA resulting in elevated plasma levels and an increased risk of bleeding (89). The ultimate version of this is during the anhepatic phase of liver transplantation when tPA clearance is almost eliminated and levels rise 10-fold or more (90).

Reduced levels of active tPA are most often associated with increased levels of the tPA inhibitor PAI-1. Increased PAI-1 is associated with an increased risk of arterial thrombosis including stroke and myocardial infarction. PAI-1 is produced in the liver and adipose tissue. Most patients with increased PAI-1 are obese with type 2 diabetes or the insulin resistance syndrome (91). PAI-1 levels in this case are correlated with intra-abdominal fat mass, increased fasting insulin, glucose, and triglycerides. Weight loss, exercise, and drugs that increase insulin sensitivity like metformin reduce PAI-1, insulin, glucose, and triglyceride levels (92,93).

WOUND REPAIR

Disorders of hemostasis are characterized not only by prolonged bleeding, but also by slow wound healing. Hemostasis can affect wound healing in at least two ways: normal activation of hemostasis directly stimulates wound healing, while inadequate hemostasis leading to formation of wound hematomas and the greater risk of infections that accompany hematomas may slow wound healing. In general, wound healing occurs in three broad stages: attraction and migration of monocytes and neutrophils to an injured area over the first 1 to 3 days; activation of macrophages and fibroblasts by cytokines leading to synthesis of collagen and other extracellular matrix materials and to proliferation of fibroblasts, a process of 14 to 21 days; and the long-term remodeling and consolidation of new collagen and other tissue constituents over a period of months. Activation of hemostasis, particularly platelet plug formation, plays a primary role in initiating the first stage and perhaps the second of wound healing (94,95). Activated platelets initiate wound healing and angiogenesis by the release of growth factors and chemotactic factors from their alpha granules. Platelet-derived growth factor is central to the wound healing process. It is strongly chemotactic for monocytes and neutrophils, attracts fibroblasts and smooth muscle cells, stimulates the proliferation of smooth muscle cells, activates neutrophils and monocytes, and induces genes likely to further promote wound repair. Other links between hemostasis and wound healing include thrombin which is mitogenic for fibroblasts, macrophages, and smooth muscle cells, and factor XIII deficiency, a bleeding disorder resulting in failure of fibrin cross-linking in which wound healing is often delayed even though platelet function, thrombin generation, and fibrinolysis are all normal.

ALTERATIONS IN HEMOSTASIS

During pregnancy, factor VIII, von Willebrand factor, and fibrinogen levels all rise in the mother, peaking in the third trimester (96). Presumably higher levels of coagulation factors at the time of birth reduce the risk of bleeding. Levels of these same factors also increase as part of the acute phase response associated with infection, inflammation, and cancer. At birth in normal full-term infants the vitamin K dependent factor levels VII, IX, X, prothrombin, protein C, and protein S are on average about 50% of adult levels (97). These factor levels do not rise to adult levels until approximately 1 year of age or more. Levels of these proteins are even lower in premature infants (98). Acquired causes of low coagulation factor levels and platelet counts include blood loss and consumption due to major trauma, infection, or extensive cancer. When tissue damage is extensive or widespread, as occurs in sepsis, shock, or major trauma, endothelium may be activated and disrupted throughout the vascular system leading to widespread exposure of collagen and tissue factor, down regulation of normal endothelial antithrombotic mechanisms, and up regulation of prothrombotic endothelial functions. This can lead to disseminated intravascular coagulation, where the normal regulation of clotting is disrupted and both procoagulant factors such as fibrinogen and platelets as well as anticoagulant factors like antithrombin and protein C are rapidly consumed resulting in platelet deposition and fibrin formation throughout the vascular system.

Low levels of coagulation factors or platelets are associated with an increased risk of bleeding. Factor levels greater than 50% of normal, fibrinogen about 1 mg per mL and platelet counts about 50,000–100,000 per μL are usually sufficient for surgical hemostasis in uncomplicated cases. Postoperatively, fibrinogen, factor VIII, and von Willebrand factor all increase. These changes slowly return to preoperative levels over 1 to 3 weeks. While useful in maintaining hemostasis after surgery, increased postoperative factor levels may also raise the risk of venous thrombosis.

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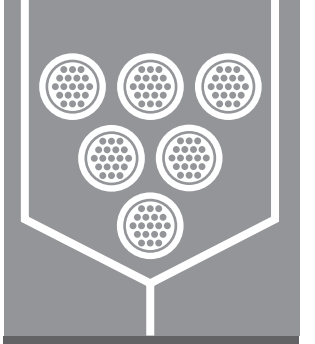

8

Platelet Physiology: Cellular and Protein Interactions

Christine S. Rinder

As early as 1875, Zahn (1) observed that bleeding from a blood vessel injury was initially blocked by a white thrombus. By the 1880s, Bizzozero (2) and Hayem (3), independently, wrote about a blood particle they called a hematoblast or platelet, a colorless corpuscle smaller than red or white cells. Bizzozero theorized that the accumulation of this corpuscle at a site of bleeding might account for Zahn's white thrombus. This colorless corpuscle was often thought of as a sticky, anucleate cell fragment that provides a temporary plug in vessel holes much like masking tape. Only in recent years have scientists and clinicians alike come to recognize the platelet's critical role in orchestrating the complex array of processes leading to hemostasis.

Keeping a balance of procoagulant and anticoagulant function is fundamental to maintenance of blood flow throughout the circulation; however, in the arterial circulation in particular the consequences of a hemostatic derangement may be life-threatening. Given the blood flow velocity in this pressurized system, loss of the endothelial cell barrier can give rise to major blood loss in a short period of time (4). Reestablishment of vascular integrity requires rapid, effective plugging of the arterial tear, both to halt blood loss and also to prevent extension of the vessel rent by the force of arterial pressures. This plug then requires coordinated operation of the soluble coagulation system to buttress the clot by fibrin deposition. By the same token, as vigorous as are the processes acting to stop arterial bleeding, so must the systems operating to limit the arterial clot growth be potent and error-free. Indeed, were arterial clots to form without opposing forces constraining their growth, every arterial bleeding site would, once the hemorrhage was contained, progressively develop into an occlusive arterial thrombus, threatening downstream tissue with equally catastrophic ischemia. It is in the arterial circulation that platelets are most challenged and where dysfunction is most evident. In arterial vessel injury, it falls to the platelet to rapidly develop the platelet plug that will abrogate the ongoing bleeding and immediately thereafter, orchestrate the development of a lysis-resistant, platelet-rich, fibrin clot. Accordingly, the discussion that follows will focus on platelet physiology under arterial flow conditions, where platelet number and function are absolutely essential for maintenance of hemostasis and blood flow.

PLATELET PHYSIOLOGY

Structure of the Resting and Activated Platelet

Platelets are anucleate cells released from megakaryocytes in the marrow and to a lesser extent, the lung, that circulate in the blood for about 7 to 10 days. The resting platelet is disc-shaped with a smooth membrane except for invaginations known as the open canalicular system that permit small molecules' entry into the elaborate network of internal membranes (5) (Fig. 8.1). Inside the cell are 2 types of granules. The most numerous granule, the α-granule, contains adhesive ligands and growth factors and is the granule

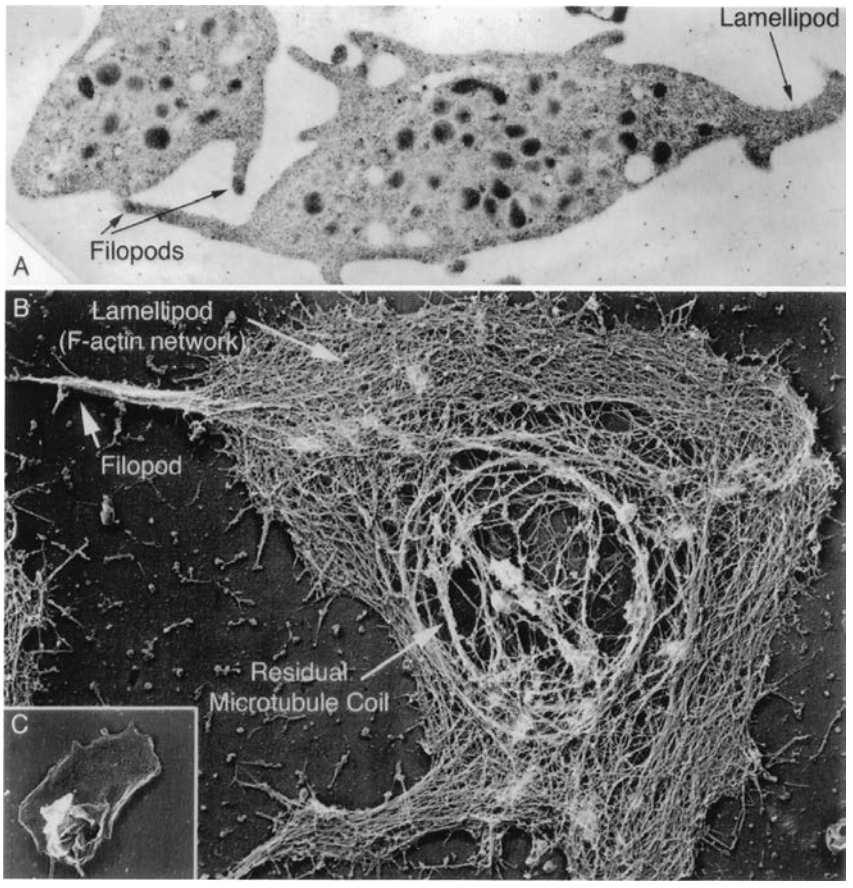

Figure 8.1 Structure of the active platelet in the electron microscope. **A:** Thin section through platelets activated with thrombin for 15 sec. At this time point, the cells have elaborated primarily filopods. **B:** Cytoskeleton of the active platelet. Platelet spreading is accompanied by a striking reorganization of the actin cytoskeleton. Regions that correspond to lamellae are found densely filled with a three-dimensional network of short actin filaments. **C:** Surface of the active platelet. (Reprinted with permission from Hartwig JH, *Platelets*. Amsterdam, Netherlands: Academic Press; 2002:43.)

most readily released from the platelet by weak agonists or low concentrations of more potent platelet activators. The second granule, the dense granule, so called because of its appearance by electron microscopy, is less abundant than the α-granule. Dense granules contain calcium, the soluble platelet agonists, ADP and serotonin, agents critical to recruiting additional platelets to a developing platelet plug at sites of bleeding. Release of the dense granule requires a more aggressive platelet stimulant or a combination of agonists. *Platelet activation* in the past was typically treated as though it were a single event, a unimodal response to all levels of stimulation, akin to a light switch that is either on or off. Instead, we now know the platelet has a remarkable repertoire of changes that may be both partial and reversible, depending on the strength and circumstances of their stimulation (6). To avoid confusion in the discussion that follows, however, platelet activation will be defined as the platelet response to maximal stimulation. However, the reader should bear in mind that more graded activation states are possible in response to lesser stimuli, and many in vivo activation events fall short of the threshold needed to give rise to an effective platelet plug.

Platelet activation is comprised of a series of events beginning with shape change. The stimulated platelet loses its discoid shape and develops a more spherical shape, which progressively flattens out, extending fingerlike projections (filapods) laterally. During this flattening process, the granules and other organelles cluster at the center of the cell (7). This cell spreading is accompanied intracellularly by filament assembly, culminating in extrusion of the granule contents into the extracellular milieu via the open canalicular system. The major platelet membrane glycoprotein, $\alpha_{IIb}\beta_3$ (GPIIb/IIIa), in addition to undergoing the conformational changes that permit binding to fibrinogen at the cell surface (8), is also anchored in the cytosol to actin filaments (9) which enable the platelet to develop the force necessary for clot retraction.

RHEOLOGY OF ARTERIAL BLOOD FLOW

Blood moving through a vessel at the velocities typical for arterial blood flow can be modeled as concentric rings of fluid moving at different velocities (Fig. 8.2). The central core of fluid moves at the highest velocity. Sheathing this

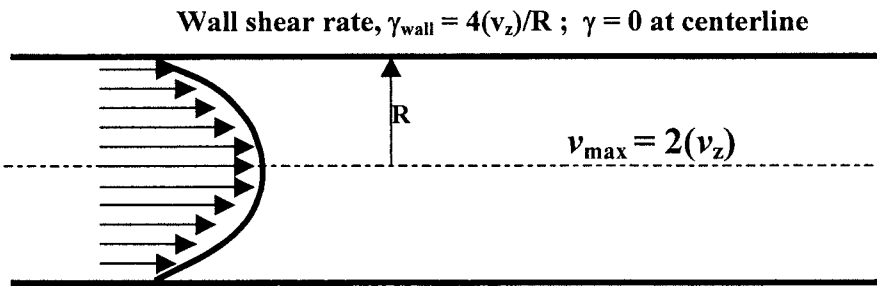

Figure 8.2 Physical properties of fluid flow through a cylinder. Velocity and shear rate as a function of radial distance for pressure-driven flow of fluid behaving as a Newtonian liquid in a cylinder. The velocity is greatest at the center and decreases with radial distance from the center. The shear is greatest at the wall and approaches zero at the center.

central, fast-moving fluid core is a ring whose velocity is slightly slower. Immediately outside that ring is another that moves still more slowly, as does each successive ring of blood all the way out to the vessel wall. The shear rate, γ, is a measure of how rapidly these adjacent fluid layers slide past each other, and is expressed in inverse seconds (sec^{-1}) (10). Shear rate within the vessel at a radial point, r, is defined according to the following equation:

$$\gamma = dv_z/dr = 4(v_z)r/R^2$$

where v_z is the mass average velocity, and R is the vessel radius. The shear rate is greatest at the vessel wall, ($\gamma_{wall} = 4(v_z)/R$) and zero at the center of the vessel. Given that wall shear rates are inversely proportional to the vessel radius, R, shear is greatest in arterioles, and decreases in progressively larger arteries, reaching a still-forceful nadir in the major arteries (Table 8.1). The velocity of blood flow in the venous system is low enough that shear force has a virtually negligible role in affecting venous blood flow. In the arteries, however, shear forces play an important role in determining how the different cell types travel. The red and white cells, because of their greater size (and momentum), are least affected by shear rate, and accordingly travel in the center of the vessel where the velocity is maximal, a phenomenon known as coaxial flow. Shear causes the smallest cells, the platelets, to be pushed to rings more lateral to the red and white blood cells and nearer the vessel walls, at a slightly reduced velocity. Thus, the dynamic properties of arterial blood flow serve to concentrate the platelets adjacent to the EC layer, positing them ready to adhere to any breach in the vessel wall.

TABLE 8.1
TYPICAL WALL SHEAR RATES FOR VESSELS OF DIFFERENT DIAMETERS

Blood Vessel	Mean Wall Shear Rate (s^{-1})
Large arteries	300–800
Arterioles	500–1,600
Veins	20–200
Stenotic vessels	800–10,000

Platelet Adhesion

Although platelets traveling near the arterial vessel wall are poised to respond to exposed subendothelium, the obligate physical and biochemical changes associated with platelet activation as described above make the classical platelet response sequence of platelet stimulation to platelet activation to platelet adhesion, far too slow for the immediacy of the need. To that end, the platelet takes advantage of the high shear properties of arterial blood flow to facilitate its own arrest at a site of arterial bleeding. Essential to this process is the multimeric protein, von Willebrand factor (vWF) (11). The base unit of vWF is synthesized by ECs as a polypeptide of 2,813 amino acids, and these base units are then joined by disulfide bonds into dimers in the endoplasmic reticulum. These dimers are then linked through successive N-terminal disulfide bonds into multimers, ranging in mass from 500 to 20,000 kDa. Some of these large vWF multimers are released in a constitutive fashion into the plasma, some are released in an abluminal direction into the vessel adventitia, and the remainder are stored in EC granules known as the Weibel-Palade bodies. The multimeric nature of vWF is critical to its ability to initiate platelet adhesion at a site of bleeding (12). In the plasma, vWF circulates as a loosely coiled molecule with an apparent diameter of 200 to 300 nm, showing no affinity for cocirculating platelets. Disruption of the EC layer exposes subendothelial collagen that either binds to plasma vWF or has vWF prebound to it. Under the influence of the high shear present along the vessel wall (a threshold value of 1000 sec^{-1} is required), this tethered vWF uncoils to lengths as great as 1,300 nm. The uncoiling of vWF is thought to expose a hitherto cryptic domain in the A1 region of the molecule, a domain with instantaneous affinity for the platelet surface receptor, glycoprotein (GP)Ibα (Fig. 8.3). The coupling of this vWF domain to GPIbα is characterized by a high rate of bond formation. This fast-on binding tethers the platelet to the exposed subendothelium in the face of the high velocity blood flow

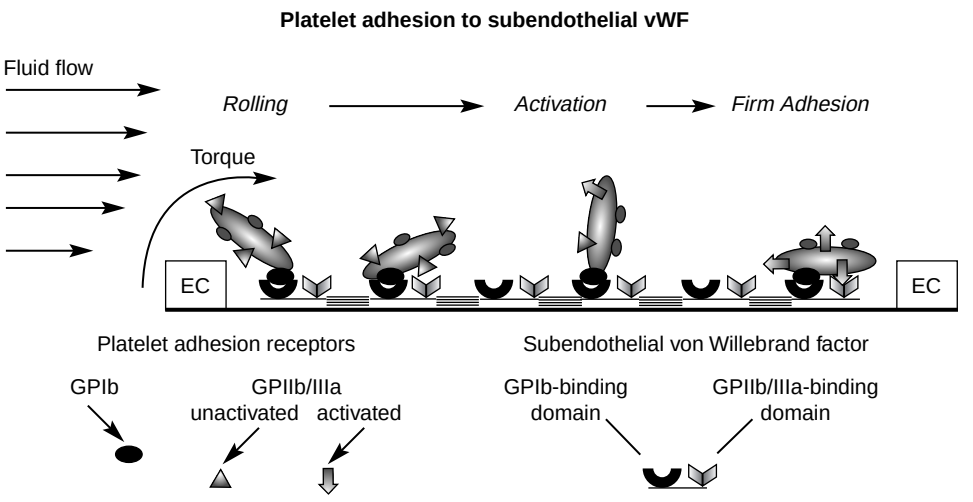

Figure 8.3 Platelet adhesion to subendothelial vWF. Arterial injury disrupts endothelial cell (EC) lining of vessel, exposing adherent multimeric von Willebrand factor (vWF) whose conformation is elongated due to the high wall shear present. A passing, unactivated platelet binds to a site on vWF exposed by the shear via its receptor, platelet glycoprotein GPIb. The high shear causes the GPIb-vWF bond to break, allowing the platelet to move on, albeit more slowly, but the adhesive event has activated the platelet. A second platelet receptor, GPIIb/IIIa, undergoes a conformational change that allows it to bind to a distinct domain on vWF, allowing for shear-resistant adhesion of the platelet.

that would sweep the platelet past the bleeding site. The relatively weak strength of this adhesive bond is soon overcome by the local shear force, however, and the platelet moves on, albeit now at a slower velocity and still in proximity to the vessel wall (13). In addition to slowing the platelet's velocity, the vWF-GPIbα interaction causes a transmembrane signaling event that stimulates the platelet to become activated. This platelet activation process includes granule release and conformational changes in a second platelet receptor, GPIIb/IIIa, that allow it to bind to a different domain also present on vWF. Unlike the initial vWF-GPIbα interaction, however, the binding of GPIIb/IIIa to vWF has sufficient strength to resist the local shear forces, such that the platelet is finally arrested on the surface of this tethered ligand (14). The larger vWF multimers are more successful at this sequence of events, permitting both steps to occur on a single vWF multimer. So the initial interaction of GPIbα with vWF has a dual role, one of slowing the platelet and another of inducing the conformational changes that allow it to be cemented to the exposed subendothelium. This sequence of events is repeated over and over until the exposed subendothelium is covered by a monolayer of activated platelets. Patients deficient in either vWF (von Willebrands disease) or its platelet receptor, GPIb, (Bernard-Soulier Syndrome) (15) demonstrate defective platelet adhesion to exposed subendothelium at shear rates in the range of 1,500 sec^{-1}, rates typical for arterioles and stenotic vessels, and both can be associated with significant perioperative bleeding.

Platelet Aggregation

Once the exposed subendothelium is covered by a platelet monolayer, the next step is extension of the platelet plug by recruiting additional platelets to its surface. Platelet recruitment is dependent on stimulation of passing platelets by agonists released from the activated platelets in the monolayer (16). These agonists include ADP and serotonin, released from the dense granules, and thromboxane A_2 released from the platelet cytosol. As these second line platelets become activated, their GPIIb/IIIa also undergoes the conformational change that allows it to bind a bridging ligand, in this case either vWF or fibrinogen, already bound to GPIIb/IIIa on an adherent platelet (17). Thus, a platelet-ligand-platelet matrix is formed at the monolayer surface, with either vWF or fibrinogen serving as the bridging ligand. In vitro studies of platelet aggregation under low flow suggest that fibrinogen, perhaps because of its abundance, is the major adhesive ligand participating in matrix formation in venous clots; at higher velocity flow, however, both fibrinogen and vWF take part in the platelet-ligand-platelet aggregation that builds up the platelet plug (18). It is this stage of platelet plug formation that is inhibited by the platelet antagonists, aspirin and clopidogrel. These agents limit extension of the platelet plug by decreasing recruitment of passing platelets by platelet-released thromboxane A2 and ADP, respectively, with the aspirin inhibiting thromboxane A2 release and the clopidogrel inhibiting binding of ADP to its receptor.

Mechanisms to Prevent the Platelet Plug from Continued Growth

This repetitious cycle of platelet activation to platelet activation to platelet activation, if unchecked, could cause the platelet plug to develop into an occlusive thrombus. The systems that work to limit growth of the platelet aggregate can be divided into two types. One type relies on healthy EC at the margins of the vessel tear releasing platelet inhibitors that prevent the platelet plug from encroaching

on portions of the vessel wall with intact endothelium. The weak platelet inhibitors, nitric oxide and prostacyclin, released by healthy EC into their microenvironment of the vessel wall stimulate cyclic GMP and AMP formation, respectively, in the platelet cytosol, reversibly blunting its response to platelet agonists and inhibiting adhesion. In addition, healthy ECs release an ecto-ADPase, (4) which inactivates platelet-released ADP, also preventing activation of platelets in its microenvironment.

A second regulatory mechanism limiting platelet plug growth operates by limiting the availability of the larger vWF multimers that are critical to platelet adhesion at high shear. A recently identified protein known as von Willebrand factor cleaving protease (vWF-CP), or ADAMTS-13, enzymatically reduces the larger vWF multimers into smaller, less hemostatically effective forms (19). Synthesized by the liver, this protease circulates in normal blood flow without any affinity for co-circulating vWF. However, it is hypothesized that as the platelet plug grows and progressively narrows the arterial lumen, the shear rate increases accordingly. For the developing platelet plug, as the shear increases, so does its dependency on large vWF multimers to continue to grow. If unchecked, the sequence of platelet slowing—platelet activation—platelet adhesion that permitted the initial monolayer to form in the face of high shear would be continuously repeated at the surface of the platelet plug until it encroached on the vessel lumen. However, as described above, multimeric vWF uncoils at high shear, exposing cleavage sites for vWF-CP (20). The smaller vWF molecules produced by this enzyme do not support platelet adhesion at high shear, thus checking growth of the platelet plug short of vessel occlusion. The importance of this mechanism at limiting arterial thrombosis is illustrated by thrombotic thrombocytopenic purpura (TTP), a syndrome characterized by loss of vWF-CP activity leading to thrombosis of the microvasculature and larger arteries, ultra-large vWF multimers in the plasma, and consumption of platelets. Thus, a deficiency of this critical regulator of platelet plug growth allows the development of multiple thrombi occurring in vessels characterized by high shear.

INTERACTIONS BETWEEN PLATELETS AND THE SOLUBLE COAGULATION SYSTEM

The next stage in the formation of a hemostatically effective clot is deposition of fibrin at the surface of the platelet plug. Platelets play a vital role in the effective coordination and acceleration of the soluble coagulation system (21,22). Following development of an occlusive platelet plug, the platelet surface continues to be critical to facilitating the enzymatic reactions that culminate in fibrin deposition. Whether in the setting of brisk arterial flow or the more leisurely flow of the venous system, the activated platelet: (a) provides membrane receptors that arrest the procoagulant zymogens and their enzymatically active products at the bleeding site, (b) releases Factors V, XI, XIII, and fibrinogen from intracellular sources, thereby enriching their local concentration, (c) provides external membrane phosphatidylserine, a negative phospholipid essential for the tenase and prothrombinase complexes, (d) assembles the enzyme complexes in a spatial orientation that optimizes their kinetics, and (e) protects bound coagulant enzymes from inhibition/inactivation.

Fifty years ago, two groups simultaneously described the waterfall or cascade model (Fig. 8.4) of soluble coagulation (23,24). This model allowed great strides to be made in identifying the series of proteolytic reactions that culminate in fibrin deposition. The cascade model recognized that anionic phospholipids, phosphatidylserine in particular, were required for optimal function of most of the enzymatic steps. Platelets were identified as a source of this negative phospholipid, which increases from about 2% of the surface phospholipid to as much as 12% upon

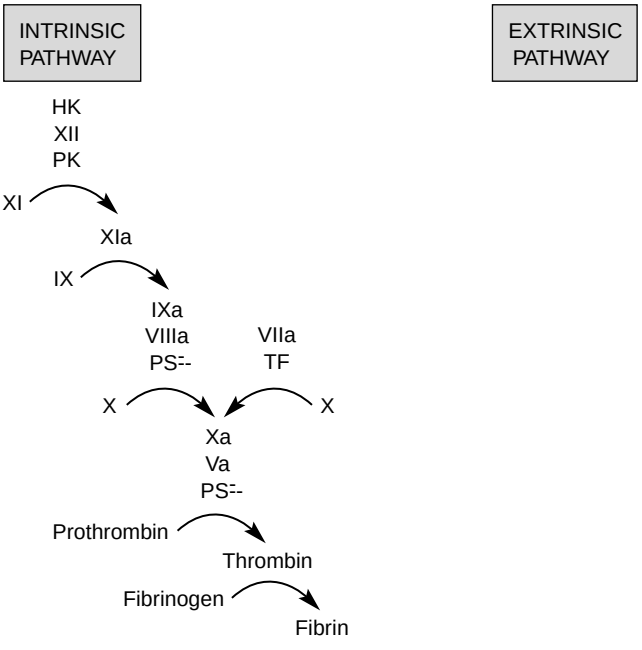

Figure 8.4 The cascade or waterfall model of coagulation. This intrinsic pathway consists of high molecular weight kininogen (HK), prekallikrein (PK), and factors XII, XI, IX, and VIII. The extrinsic pathway consists of tissue factor (TF) and factor VII, and the common pathway, factors X, V, prothrombin, and fibrinogen, culminating in generation of thrombin and fibrin. The activated form of these factors is indicated by adding the letter "a" as a suffix. Reactions accelerated by the presence of a phosphatidylserine surface (PS).

platelet activation (25). Indeed, serving as a phosphatidylserine source was thought to be the platelet's *only* contribution to soluble coagulation, and purified lipid was eventually substituted for activated platelets in the PT/aPTT assays that came to be the gold standard for measuring soluble coagulation. The results generated by these assays dovetailed well with the then-accepted model of coagulation that featured two converging pathways, the extrinsic and intrinsic pathways (Fig. 8.4). Although this model is feasible when dosing anticoagulants like heparin and coumarin, it falls short of explaining a number of clinically important scenarios. Most glaring was its inability to explain why patients with hemophilia A or B, defective only in the intrinsic portion of coagulation, had such a high bleeding risk. Why could hemophiliacs not just ramp up their thrombin generation via the extrinsic pathway, ultimately achieving hemostatically effective fibrin deposition? Another inexplicable finding was that patients with a complete absence of factor XII and drastically prolonged aPTT's could undergo major surgery without any discernible increase in bleeding.

Recent advances in cell-based research models have made significant strides in clarifying the dynamics of coagulation (22,26). Experts agree that in vivo coagulation follows exposure of the blood to a source of tissue factor (TF), typically on the surface of a fibroblast coming into contact with blood via a break in the vessel wall. The intrinsic, or contact, pathway of coagulation has no role in the earliest events in clotting. Reminiscent of the two-stage process allowing platelet adhesion under high shear, TF-initiated coagulation also has two phases; one, an *initiation* phase and a second referred to as the *propagation* phase (Figs. 8.5 and 8.6) (27–29). The initiation phase begins as the exposed TF binds to factor VIIa, picomolar amounts of which

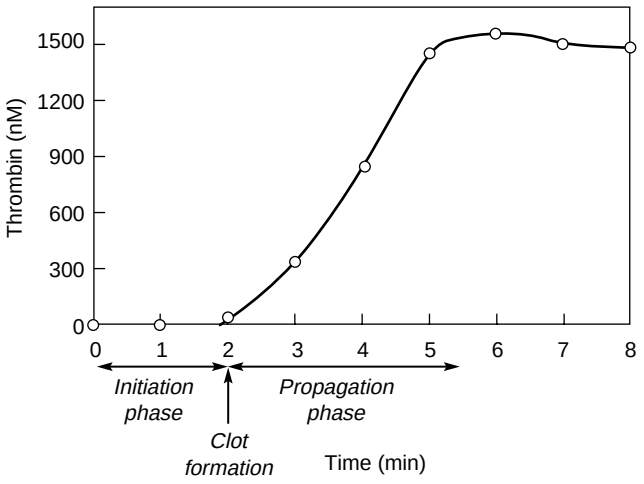

Figure 8.5 Thrombin generation over time in a synthetic plasma model system. Thrombin generation is initiated with addition of tissue factor to synthetic plasma, and thrombin generation measured over time. Thrombin generation can be divided into the initiation phase and progagation phase with clot formation occurring at the inception of the propagation phase. (Reprinted with permission from Butenas S, Veer CVT, Mann K. Evaluation of the initiation phase of blood coagulation using ultrasensitive assays for serine proteases. *J Biol Chem.* 1997;272:21527–21533.)

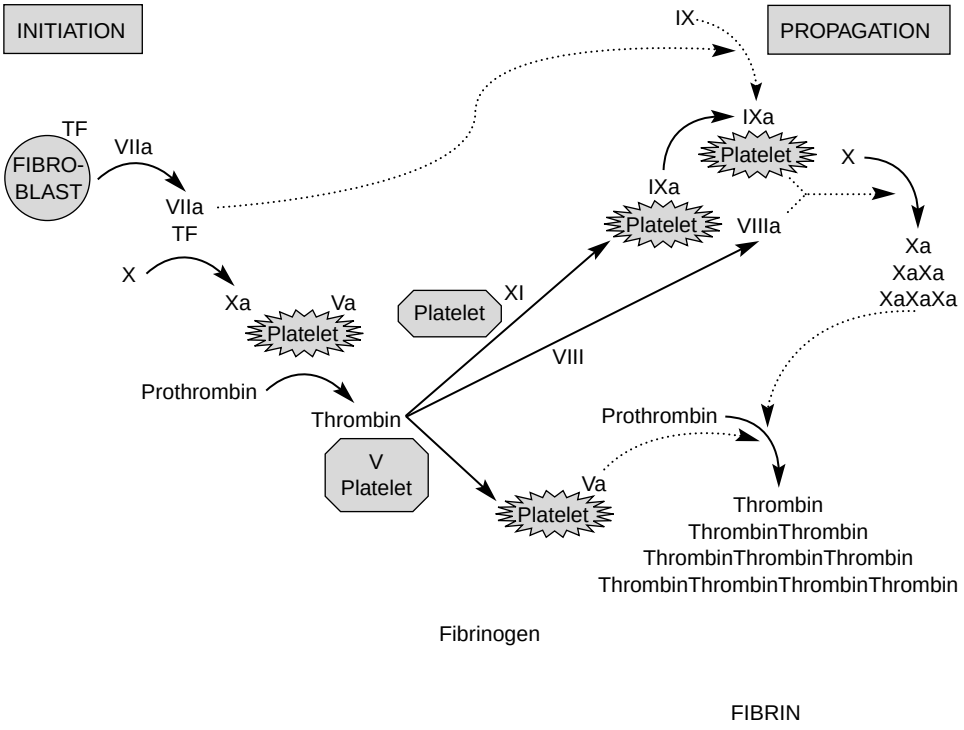

Figure 8.6 Two-phase model of coagulation. In the initiation phase of coagulation, tissue factor (TF) exposed on a subendothelial fibroblast after vessel injury complexes with small amounts of factor VIIa present in the circulation. This complex then activates a small amount of factor X to Xa in the presence of an activated platelet. The platelet-bound Xa converts a tiny amount of prothrombin to thrombin. This small amount of thrombin then sparks the propagation phase of coagulation. Thrombin activates factors XI, VIII, and V at or near the activated platelet. Factor IX is activated by either factor XIa or the TF-VIIa complex. Factor IXa complexes with the factor VIIIa activated by thrombin, and on the platelet surface generates factor Xa with remarkable kinetic efficiency. The platelet-bound factor Xa complexes with factor Va, which converts prothrombin to explosive amounts of thrombin. This thrombin in turn converts fibrinogen to fibrin, thereby sealing the clot beneath.

are present in the circulation at all times. This factor VIIa-TF complex catalyzes the conversion of small amounts of factor X to Xa, which in turn generates nanomolar amounts of thrombin. The platelet's role in this initiation phase is relatively minor; in the model systems, changes in platelet number have no effect on the time to thrombin appearance unless the count falls below 25,000 per μL, which appears to be the critical threshold for even these tiny amounts of thrombin to be generated. Similarly, in a TF-initiated whole blood assay, clotting times were unchanged with platelet counts as low as 50,000 per μL, yet counts in the range of 10,000 per μL produced a significant prolongation of the clotting time.

It is worth noting that most of the commonly used laboratory tests of soluble coagulation measure the kinetics of the initiation phase only (27). The prothrombin time (PT) and activated partial thromboplastin time (aPTT) both have as their end points the first appearance of fibrin gel, which occurs with less than 5% of the reaction complete. Thus, the fibrin clotting that signals completion of the test occurs when only minimal levels of prothrombin have been activated. These tests are sensitive in detecting congenital abnormalities associated with hemophilia A, B, and C (Factor XI deficiency), and in guiding traditional anticoagulant therapy; however, as a model of the entire sequence of events necessary for effective hemostasis, they measure only the earliest steps in the process. They fail to detect the important, platelet-dependent effects on total thrombin generation that clearly result from thrombocytopenia and potent platelet inhibitors like prostaglandin E1 and the GPIIb/IIIa antagonists, abciximab and eptifibatide.

The seemingly trivial amount of thrombin formed during the initiation phase sparks the inception of the propagation phase, successful completion of which culminates in explosive thrombin generation, and ultimately, fibrin deposition at the surface of the platelet plug. More than 96% of the total thrombin that is generated during clotting occurs during the propagation phase. It is in the propagation phase of coagulation that the activated platelet membrane takes on critical importance.

Thrombin generated during the initiation phase is a potent platelet activator, thereby providing both the activated platelet surface membrane and platelet-released factor V (which is promptly activated to Va by thrombin) in abundance. Factor VIII, conveniently brought to the bleeding site by its carrier, vWF, is also activated by thrombin, a step which causes its release by vWF. FVIIIa then complexes with the picomolar amounts of factor IXa also generated by the TF-VIIa complex during the initiation phase. Formation of the FVIIIa-IXa complex on the platelet surface heralds the switch of the primary path of FXa generation from the TF-VIIa complex to the intrinsic Xase. This switch in pathways is of significant kinetic advantage, with the intrinsic Xase complex exhibiting approximately 50-fold higher efficiency compared the extrinsic Xase generation. The bleeding diathesis associated with hemophilia A and B is testament to the physiologic importance of the exuberant thrombin generation occurring during the propagation phase (30). While congenital deficiencies in Factors VIII and IX prolong the aPTT, a measure of the initiation phase of clotting begun by an in vitro artifact, it is the thrombin generation in the propagation phase, a function not evaluated by the aPTT, that is most impaired.

Assembly of the Xase and Prothrombinase Complexes on the Activated Platelet Surface

The activated platelet expresses receptors for factors VIIIa, and IXa. The zymogens for each of these factors also have affinity for the activated platelet membrane, however the active enzymes show fivefold and 10-fold higher affinity, respectively, and there are approximately twice the number of factor VIIIa binding sites compared to those for factor VIII. Binding of the active proteases, VIIIa and IXa, together with negatively charged phosphatidylserine on the activated platelet membrane enhances the binding of their substrate, factor X. The binding of each of these proteases increases the kinetics of their contribution to factor X activation, such that the functional consequences of the assembly on the entire platelet membrane is an unbelievable 13-million-fold increase in catalytic efficiency (28). The kinetics studies where these numbers were generated are performed under static conditions and cannot gauge the kinetic advantage provided by a platelet membrane in the face of flow. The chances that an effective fibrin clot could form under arterial flow conditions *without* an activated platelet membrane stretch the limits of improbability.

Assembly of the prothrombinase complex is similarly dependent on the activated platelet surface for optimum activity. Like the tenase complex, the membrane-bound prothrombinase complex promotes prothrombin activation with a rate enhancement 300,000-fold higher than free factor Xa acting on prothrombin formed in solution. Platelet-bound factor Xa is the rate-limiting reagent in prothrombin cleavage. The exact platelet binding site for FXa is controversial, but is dependent on both platelet-bound factor Va and a membrane protein known as effector cell protease receptor-1 (EPR-1) (31). Platelet-bound factor Va comes from both plasma and platelet-released stores, although there is some evidence that the activity of the latter is actually more critical to normal hemostasis. A congenital bleeding disorder known as Factor V_{Quebec} shows a very mild deficiency in plasma factor V levels (about 70%), severe deficiency in platelet factor V levels ($<5\%$) and a marked deficit in prothrombin activation (32). The substrate for this enzyme complex, prothrombin, binds to

GPIIb/IIIa on both activated and unactivated platelets, potentially providing a source for thrombin generated in both the initiation and propagation phases of clotting.

Factor XIa—Its Role in Soluble Coagulation

Another clinical conundrum that has been difficult to reconcile with the cascade model of coagulation is the variable hemostatic effect of hemophilia C, a congenital factor XI deficiency, with about 50% of these individuals displaying severe posttraumatic or postsurgical bleeding, and the remainder exhibiting no bleeding tendency whatsoever (30). This variability stands in sharp contrast to the supposed factor XI activator, factor XII, whose deficiency is never associated with bleeding. Evidence is growing that the role of factor XI in normal coagulation comes as a means to further amplify the propagation phase of coagulation (33,34). As noted above, levels of factor Xa are rate-limiting to the prothrombinase complex. This is particularly the case once the switch is made from extrinsic Xase to intrinsic Xase. Prior to the switch, factor IXa can be generated by the activity of the TF-VIIa complex; however the ability of this complex to sustain IXa generation is limited by its inhibitor, tissue factor pathway inhibitor (TFPI) (35). Factor XI is another zymogen that is activated by the minute amounts of thrombin generated by the initiation phase, but platelet binding is an absolute requirement for thrombin to activate FXI (34). Platelet-bound FXIa is ideally located to activate FIX, which also binds to the platelet surface. Additionally, binding to the platelet surface protects FXIa from inhibition by its inhibitor, protease nexin 2. Thus, generation of FXIa on the activated platelet would seem to be vital to providing sufficient FIXa to maintaining Xa generation via the catalytically more efficient intrinsic Xase enzyme complex. This being the case, it appears even more inexplicable that some patients congenitally deficient in FXIa *don't* bleed. Walsh et al. (33) have demonstrated that, apart from plasma sources of FXI, an alternative FXI supply is provided by the platelet membrane, both in the resting state and in increased amounts following platelet activation. There is evidence that the platelet factor XI is structurally slightly different from plasma XI, and appears to be an alternatively spliced product of the gene responsible for plasma FIX. Clinical studies suggest that, in patients with absence of plasma FXI but preserved platelet FXI, the continued activity of the latter is sufficient to preserve hemostasis. By contrast, individuals with absence of both platelet and plasma FXI appear to have severely compromised hemostasis. In addition, significant bleeding was demonstrated in one patient with normal plasma FXI but absent platelet FXI. Exactly how much each of these two pools of FXI contributes to normal hemostasis remains an open question at the present time.

Clot Protective Features of the Activated Platelet Surface Membrane

In addition to providing the means for enzyme complexes to assemble in a kinetically favorable orientation, the platelet surface membrane protects the active enzymes from inactivation by proteases that abound in the plasma. During the initiation phase of coagulation, binding of FXa to the platelet membrane protects the enzyme from inactivation by tissue factor pathway inhibitor (TFPI) and antithrombin. At normal plasma levels, both TFPI and antithrombin inhibit FXa so efficiently that the plasma half-life is 1 minute or less (36). Preservation of the small amounts of FXa that are generated during this make-or-break stage of coagulation is critical to formation of the nanomolar amounts thrombin needed to begin the propagation phase of clotting. Similarly, the thrombin formed during the initiation phase must be protected from inactivation by antithrombin. Antithrombin is present at over twice the concentration (3.2 μmol per L^{-1}) of the highest concentration of thrombin reached during the propagation phase (1.4 μmol per L^{-1}), and about 1000 times the nanomolar amounts of thrombin generated during the initiation phase. In the absence of the protection conferred by the platelet membrane, thrombin is inhibited by plasma levels of antithrombin with a half-life $<$1-minute. Thus, thrombin generated during the initiation phase is critically dependent on the activated platelet membrane for the time required to transition from the initiation phase to the propagation phase of thrombin generation. Likewise, antithrombin is unable to inhibit factor IXa in the presence of factor VIIIa and platelets, or factor Xa incorporated into prothrombinase (i.e., complexed with membrane-bound factor Va) (28).

The other critical physiologic regulator of thrombin generation is protein C. Unlike antithrombin, which circulates in an active form (albeit capable of enhanced kinetics when bound to heparin or the endogenous heparan sulfate), protein C requires activation by thrombin-stimulated EC thrombomodulin. Activated protein C (APC) limits the rate of thrombin generation by inactivating the cofactors, FVa and FVIIIa (37,38). The activated platelet membrane protects FVIIIa and FVa from inactivation by APC (39).

CONCLUSION

Hemostasis is maintained by the continued circulation of procoagulant agents in a constant state of readiness. In the arterial circulation in particular, platelets are the first responders, working to achieve a temporary platelet plug to staunch the immediate blood loss, orchestrating the assembly of additional platelets, and localizing and accelerating fibrin deposition to seal the clot. Each of these

events has one or more key steps where a minimum threshold must be reached; a go/no go point where insufficient strength of stimulation, inadequate amount of substrate, or an excess of inhibition can cause clot making to abort. The successful formation of a clot is all about kinetics, and the activated platelet membrane is vital to achieving the speed and localization needed for formation of a hemostatically effective clot. Just as important, however, are the anticoagulant systems that continuously oppose platelet adhesion to healthy endothelial cells, limit the growth of the platelet plug, and rein in thrombin generation.

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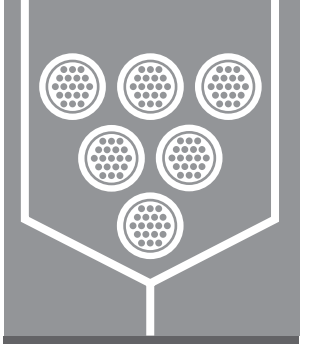

Iron Metabolism and Erythropoiesis

9

Kenneth R. Bridges

Iron is essential to life on Earth. The element's capacity to exist in two stable oxidation states, ferric (Fe^{3+}) and ferrous (Fe^{2+}), allows it to catalyze a host of vital single electron transfer reactions, such as those involved in energy generation through mitochondrial oxidative phosphorylation (1). In higher organisms, including humans, most iron exists as a component of heme, the prosthetic group of many enzymes as well as the oxygen transport protein, hemoglobin. Ferrous iron in the heme ring of deoxygenated hemoglobin has five of six coordination sites occupied, leaving a single coordination site to which molecular oxygen reversibly binds. This interaction is the key to oxygen transport by hemoglobin.

The physicochemical properties that make iron indispensable to life also create a danger. Conversion between ferrous and ferric oxidation states can generate a family of injurious compounds called reactive oxygen species. Superoxide ($\bullet O_2^-$) is an important molecule produced in a variety of chemical and enzymatic reactions. The enzyme, superoxide dismutase, converts this potentially dangerous species into oxygen and hydrogen peroxide. Catalase then converts the hydrogen peroxide into water and molecular oxygen thereby removing the danger of oxidant tissue damage posed by superoxide. Hydrogen peroxide can, however, take another pathway in which iron catalyzes the formation of the extremely reactive hydroxyl radical ($\bullet OH$) in a process called the Fenton reaction. The hydroxyl radical promotes injury through the formation of molecular cross-links in proteins, lipids, and DNA (2). These events can be catastrophic for cells and tissues.

Properly directed, however, reactive oxygen species including the hydroxyl radical can serve as powerful defense mechanisms. A prime example involves the fight against bacterial invaders. Polymorphonuclear leukocytes engulf bacteria and bath the organisms trapped in the phagosome with reactive oxygen species as part of the bacteriocidal effort (3). Compromise of this mechanism produces potentially fatal disorders, such as chronic granulomatous disease (4). In contrast, unconstrained reactive oxygen species can extensively damage cells and tissues by cross-linking DNA, lipids, and proteins. The tissue damage seen with rheumatoid arthritis derives in part from the indiscriminate generation by iron of reactive oxygen species (5,6). The Jekyll and Hyde character of iron demands delicate handling at every juncture.

Simply acquiring the iron needed for normal metabolism is a challenge. Although the element is abundant in the earth's crust, most iron exists in highly insoluble forms such as ferric hydroxide [$Fe(OH)_3$], which is common rust. Finely tuned cooperative activity involving sequential segments of the gastrointestinal tract promotes efficient iron absorption. Iron must be converted to a soluble form within the gastrointestinal tract and transported into the body proper. (The lumen of the gastrointestinal tract is actually external to the body.) Recent advances in molecular and cellular biology have clarified many of the mysteries that long surrounded the complicated process of iron absorption. Defective iron uptake, transport, or storage can impair erythrocyte production since hemoglobin is the primary destination for iron in the body.

THE COMPONENTS OF IRON HOMEOSTASIS

Some proteins involved in iron homeostasis, such as ferritin and transferrin, have long been on the cell biological

stage. Others, such as hepcidin, are recent additions to the compendium. Table 9.1 lists the proteins that contribute most prominently to iron balance along with their known functions. Many of the proteins have more than one function and more than one site of activity. Ferroportin 1, for instance, appears to facilitate iron transport from the cytosol of macrophages in addition to the listed function as a conduit for iron between gastrointestinal enterocytes and plasma transferrin. The table simplifies the more extensive information found in comprehensive reviews (7,8).

Some of the proteins in Table 9.1 indirectly influence iron homeostasis by modulating the expression or action of other proteins that handle iron. IRP-1 is a fine example of the phenomenon. This intracellular protein recognizes and binds a specific sequence, termed the IRE, in the mRNA encoding a number of iron-related proteins. IRP-1 binding to IRE sequences in the 5′ untranslated region of a message, such as that in ferritin mRNA, blocks translation into protein product. In contrast, IRP-1 binding to IRE sequences in 3′ untranslated regions stabilizes the mRNA. This is the case with the message for the transferrin receptor. Ambient iron in the cell cytoplasm alters the structure of IRP-1, thereby controlling its affinity for the IRE sequence. Therefore cells modulate the means of iron uptake (transferrin receptor) or iron storage (ferritin) in response to the concentration of intracellular iron, with IRP-1 serving as both sensor and effector (9).

The risk of iron producing unruly reactive oxygen species through Fenton chemistry is a major biological challenge. The most effective way of avoiding this danger is to couple iron with chelating compounds that form tight coordination complexes with iron's unpaired electrons. The bacterial siderophore, desferrioxamine, is an excellent example of this principle. The linear desferrioxamine molecule folds to bring multiple polar head groups into juxtaposition with ferric iron as shown in Figure 9.1. The resulting complex is extremely stable with an association constant approximating 10^{34} M (10). Most importantly, the chelated iron cannot promote the formation of reactive oxygen species.

Free iron that can catalyze the generation of reactive oxygen species is virtually nonexistent within the body. Various proteins hold iron in tight check until it is needed for specific purposes. The transport protein, transferrin, has two binding sites for iron, one at each end of the linear

TABLE 9.1
KEY PROTEINS OF IRON METABOLISM

Protein	Function
Gastrointestinal Iron Absorption	
DMT1[a] (known also as DCT1 and NRAMP2)	Conducts Fe^{2+} from GI lumen into the enterocyte; also from the endosome to cytosol in normoblasts
Dcytb[a]	Converts iron from Fe^{3+} to the Fe^{2+} that traverses DTM1
Hephaestin	Intracellular ferroxidase that facilitates iron exit from the enterocyte
Ferroportin 1	Conducts iron from enterocyte to plasma
Heme transporter	Conducts heme from GI lumen into the enterocyte
Iron Transport Between Cells	
Transferrin	Protein in plasma and extracellular fluids that transports iron between cells
Ceruloplasm	Copper transport protein that is also a ferroxidase important to the endocytosis of iron bound to transferrin
Cellular Iron Uptake	
Transferrin receptor 1	Mediates cellular uptake of iron from transferrin
Transferrin receptor 2	Uncertain function; mutation produces severe iron overload
Intracellular Iron Metabolism	
IRP-1 and IRP-2[a]	Posttranscriptional regulation of iron-related proteins including transferrin receptor 1 and ferritin
Ferritin	Iron storage protein; 24 subunit heterodimer of H and L chains
Frataxin	Mitochondrial iron homeostasis
Global Regulation of Iron Metabolism	
Hepcidin	Dampens gastrointestinal iron absorption; promotes iron retention by reticuloendothelial cells
HFE	Alters the efficiency of iron uptake from transferrin; mutations produce hereditary hemochromatosis

[a]DMT1, divalent metal ion transporter 1; Dcytb, duodenal cytochrome b; IRP, iron responsive protein

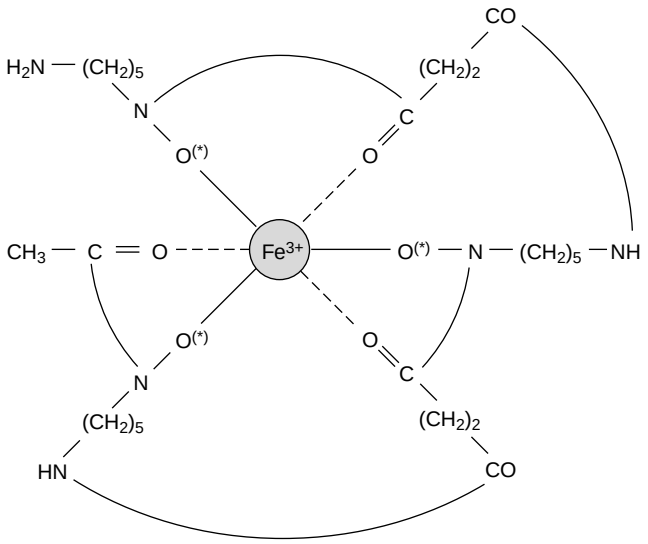

Figure 9.1 Chelation of ferric iron by desferrioxamine. The bacterial siderophore desferrioxamine forms a coordination complex with the six coordination sites of iron. The complex is extremely stable and is incapable of catalyzing free radical formation.

molecule. Under physiological conditions, the association constant between iron and transferrin is about 10^{23} M (11). The high concentration of transferrin in the plasma (approximately 40 μM) along with 50% occupancy of its iron binding sites allows the protein to mop up any unbound iron from plasma and extracellular fluids. Only the finely tuned iron release mechanism of the endosome triggered by receptor-mediated endocytosis of transferrin can pry iron from transferrin. A specialized transport mechanism then shuttles the iron from the endosome into the intracellular space.

Intracellular iron is stored in ferritin until needed for physiological purposes. Ferritin is an enormous hollow protein shell formed by 24 H-subunits or L-subunits whose ratio varies for individual ferritin molecules (12). Iron enters the ferritin shell through one of several pores and exists as a ferric/hydroxide/phosphate crystal within the ferritin vault (13). The stored iron cannot promote Fenton chemistry and poses no danger to the cell. Ferritin is an enormous potential iron reservoir with each molecule housing up to 4,500 iron atoms.

IRON UPTAKE FROM THE GASTROINTESTINAL TRACT

Humans have no physiological mechanism of iron excretion. The one milligram of iron absorbed daily from the gastrointestinal tract precisely balances daily losses due to desquamation of cells from the gastrointestinal tract, the genitourital tract and the skin. Females of reproductive age average an additional milligram of daily iron loss due to menstruation. A higher rate of iron uptake in females maintains a steady state with respect to body iron stores (14). Roughly 80% percent of absorbed iron flows to the erythron for hemoglobin synthesis. Myoglobin and iron-dependent enzymes are the destinations for most of the remaining iron, while a small amount of the mineral enters ferritin storage sites (Fig. 9.2).

A large daily flux of iron exists in the body, with the destruction of senescent red cells by tissue macrophages accounting for most of the action. Transferrin conducts iron mobilized from storage sites back to the erythron for

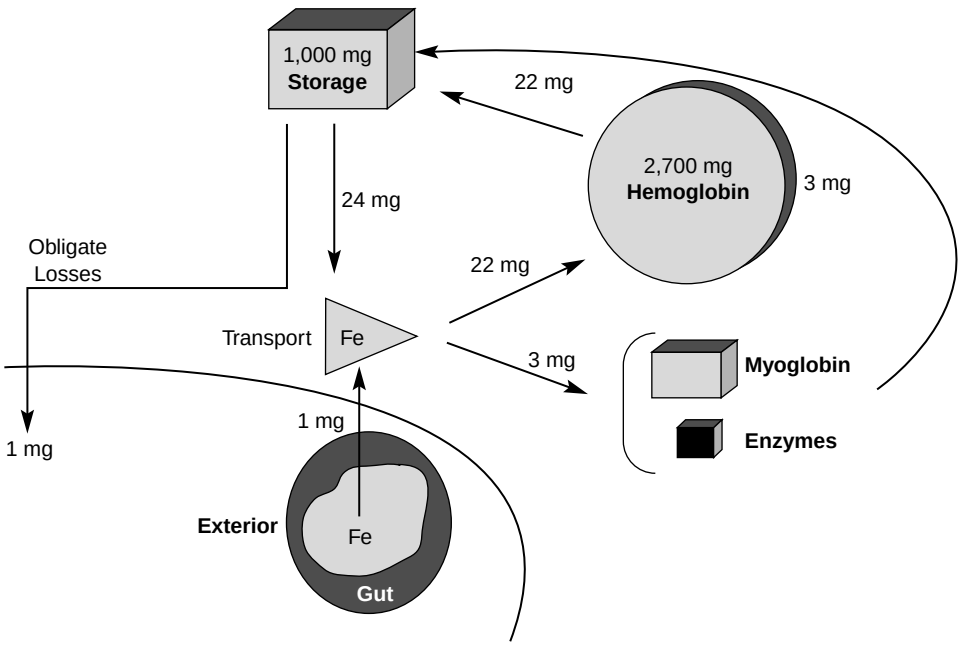

Figure 9.2 Iron homeostasis. Approximately one milligram of iron is absorbed daily from the gastrointestinal tract, which precisely balances obligate iron losses. The absorbed iron joins a large pool of iron flowing from storage sites to the bone marrow for the production of new red cells. This quantity of iron balances that entering storage sites from senescent red cells. A small amount of iron is directed to myoglobin and enzymes.

production of replacement red cells. Absorbed iron constitutes only a small fraction of the mineral involved in this daily trafficking, but is key as the counterbalance to obligate daily iron losses. When iron loss exceeds intake, due for instance to a bleeding peptic ulcer, the result is iron deficiency with anemia as the most prominent manifestation (15).

Most dietary iron consists of various inorganic salts. Heme iron is available to people with significant meat and protein in their diets. The physical state of iron determines the facility of absorption, with heme > Fe^{2+} > Fe^{3+} (16). The acid environment of the stomach increases the solubility of Fe^{3+} with consequent enhancement of overall iron absorption. The iron deficiency that frequently accompanies pernicious anemia, for instance, arises from the gastric achlorhydria produced by the disorder and is a testament to the importance of gastric acidity in iron absorption (17).

The duodenum and proximal jejunum are the sites of most iron absorption. Figure 9.3 outlines the key steps that are believed to occur in villous enterocytes. Ferric iron is first reduced to the ferrous form that is preferred valence for the DMT1 transporter. Ferritin sequesters a small quantity of the iron taken into the enterocyte. This iron is lost when the enterocyte is sloughed into the gastrointestinal lumen following its senescence thereby contributing to the obligate daily losses of the element. Most iron, however, moves from the luminal to the basolateral surface of the cell where ferroportin 1 provides a conduit into the plasma. Hephaestin is critical to the exit of iron from the enterocyte, although its precise location in the cell is unclear.

Transferrin shuttles iron throughout the body in a safe, inactive form. For most iron, the ride terminates in the bone marrow, specifically on the transferrin receptors of normoblasts. The transferrin/transferrin receptor complex is internalized by receptor-mediated endocytosis (Fig. 9.4). Acidification of the endosome contributes to the separation of iron from transferrin. The movement of iron out of the endosome into the cytosol proper again involves DMT1, possibly in concert with a ferroxidase enzyme. Iron in the cytosol quickly shuttles either to ferritin or to sites of utilization, such as the heme biosynthetic machinery of the mitochondrion. Little is know about the mechanism of intracellular iron transport.

ERYTHROPOIESIS

Red cell production, or erythropoiesis, occurs primarily in the bone marrow of the axial skeleton. Precursor cells committed to erythrocyte production move through a series of stages that end with the release of new erythrocytes into the peripheral circulation. As shown in Figure 9.5, a host of cytokines and growth factors contribute to the early steps leading to mature red cells. The main red cell growth factor, erythropoietin, acts on cells just prior to hemoglobin production in the BFU-e and CFU-e stages of development. Erythropoietin energizes the maturation process and pushes the cells to the proerythroblast stage where visible hemoglobin synthesis begins.

Figure 9.5 also highlights the interdependence of erythropoietin and iron in red cell production. In the absence of erythropoietin, maturation beyond the BFU-e and CFU-e stages is halting. The hormone both stimulates growth and

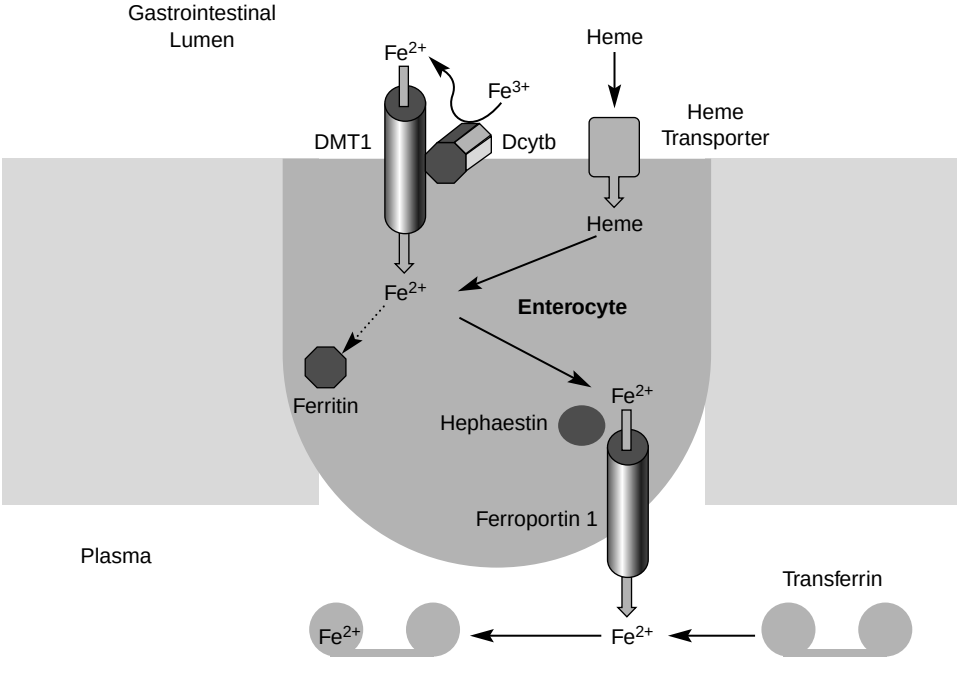

Figure 9.3 Gastrointestinal iron absorption. Ferric iron in the gastrointestinal tract (Fe^{3+}) is reduced to the ferrous form by Dcytb and transported into the enterocyte by DMT1. Most of the iron exits at the basolateral surface through the action of hephaestin and ferroportin 1. Heme is taken into the cell by a transporter that remains to be characterized. Heme oxygenase degrades the molecule and releases its iron.

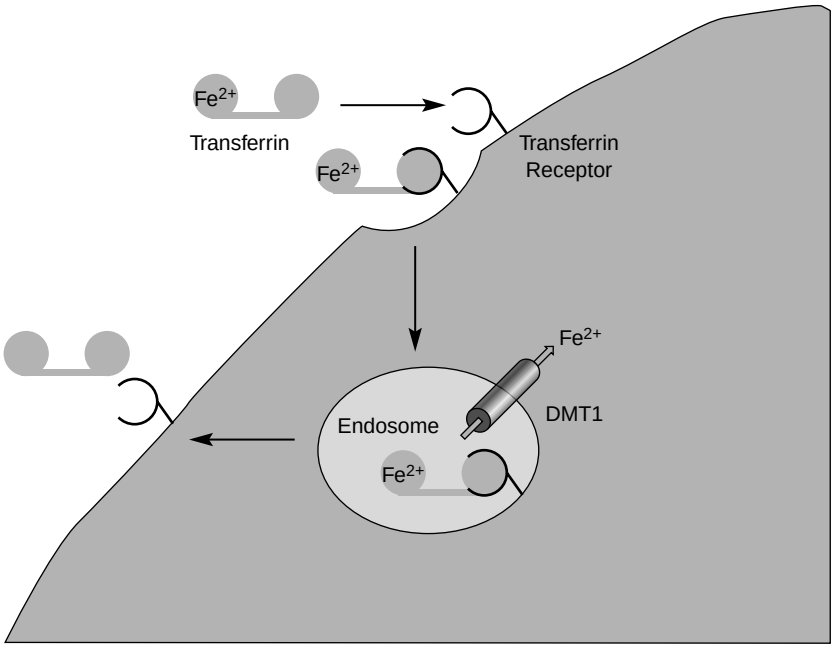

Figure 9.4 Receptor mediated endocytosis of transferrin. Iron-transferrin complex in the circulation binds to cell surface transferrin receptors. The complex is internalized by receptor-mediated endocytosis into an endosome where iron separates from transferrin and traverses to the cytoplasm proper by way of DMT1. The endosome fuses with the plasma membrane releasing the iron-free transferrin.

opposes apoptosis (18). Likewise, erythroid precursors cannot move effectively beyond the proerythroblast stage without an adequate iron supply. Inadequate iron constrains the synthesis of heme and hemoglobin effectively blocking red cell maturation.

A static image such as Figure 9.5 fails to convey the crucial role of timing as it relates to iron, erythropoietin, and red cell production. Erythropoietin primes the precursor cells for maturation, but there is a temporal window of opportunity. Iron in the form of iron-transferrin must be available within a short time of erythropoietin stimulation for cells at the BFU-e and CFU-e stages to progress in their maturation. The cells do not simply queue up in a primed state patiently awaiting the arrival of iron. When the time passes, the opportunity for maturation is gone. The timing of erythropoietin and iron delivery to cells normally is not an issue since both iron-transferrin and erythropoietin bath the precursor cells continuously. Problems can arise under aberrant circumstances such as that associated with erythropoietin replacement in renal insufficiency. This issue is revisited later in the chapter.

While all cells produce heme, its production by erythroid precursors is prodigious. Figure 9.6 is a simplified schema of heme biosynthesis. The process begins in the mitochondrion with the condensation of glycine and succinyl-CoA to form delta-amino levulinic acid (ALA) with pyridoxal phosphate as a cofactor (19). The processing of ALA then moves to the cytoplasm where serial enzymatic transformations produce coproporphyrinogen III. This molecule enters the mitochondrion where additional modifications, including the insertion of iron into the protoporphyrin IX ring by ferrochelatase, produce heme.

When the supply of iron is inadequate for the quantity of protophorphyrin that a cell produces, zinc can intercalate into the protoporphyrin IX ring in a non-enzymatic process producing zinc protoporphyrin (ZPP). ZPP does not form a stable complex with globin and cannot transport oxygen. The molecule is fluorescent, making detection a relatively simple process. ZPP is a sensitive indicator of the degree of coordination between protophorphyrin production and iron delivery to developing erythroid cells. A brief period of mismatch between the two can cause ZPP accumulation even when hemoglobin production declines only minimally.

SYSTEMIC IRON HOMEOSTASIS

Until recently, little was known about the factors that modulated critical aspects of iron homeostasis. Many conditions altered iron metabolism, but the mechanisms mediating the changes were a mystery. Gastrointestinal iron absorption, for instance, rises in the face of iron deficiency and falls with iron overload. These observations fit well with the known importance of gastrointestinal iron absorption in maintaining the balance of iron stores. Hypoxia also increases iron absorption. The speculation regarding this phenomenon posited that enhanced iron absorption facilitates hemoglobin synthesis and the production of new red cells that would eventually correct the hypoxic state. These explanations were teleologically satisfying but lacked experimental foundation.

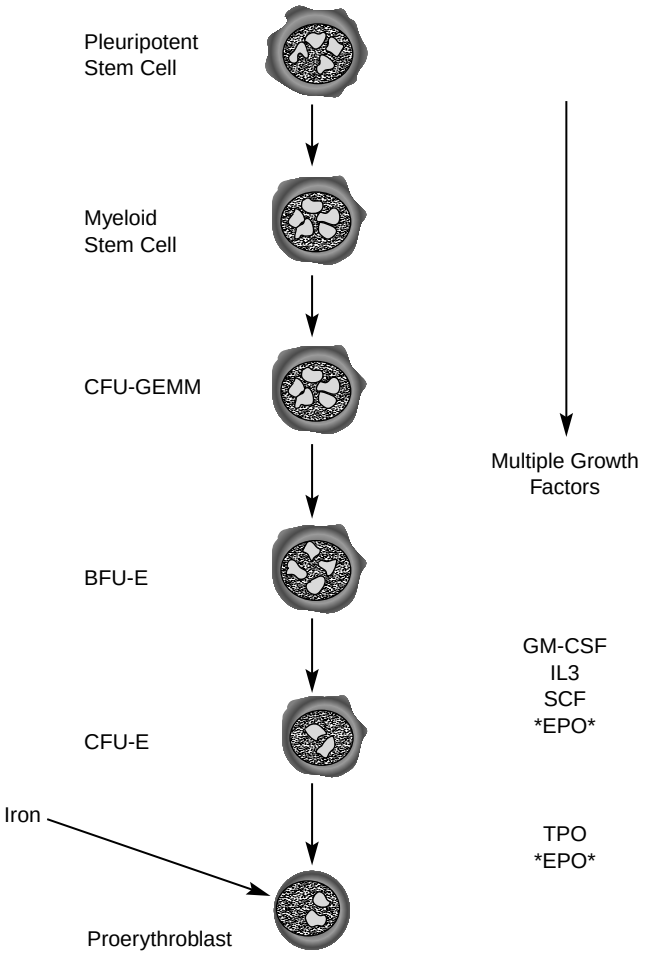

Figure 9.5 Erythropoiesis. A host of growth factors promote the maturation of the pleuripotent stem cell along the pathway that leads to the BFU-e. Erythropoietin acts on the BFU-e and the CFU-e, which move to the proerythroblast stage where hemoglobin synthesis begins and iron is required.

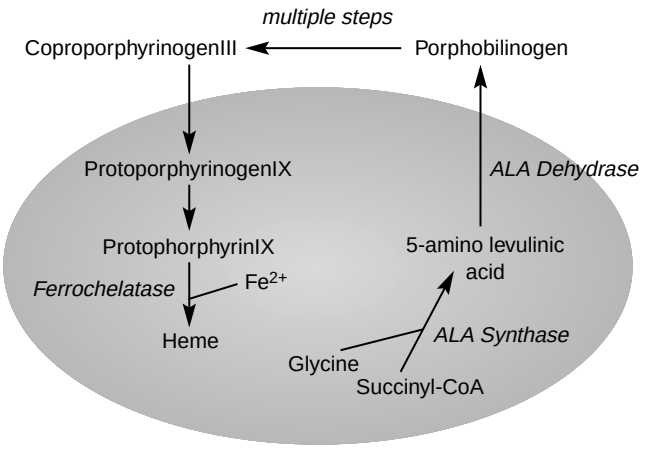

Figure 9.6 Heme biosynthesis. Heme biosynthesis begins in the mitochondrion with the condensation of succinyl CoA and glycine to form 5-amino levulinic acid. Several enzymatic steps occur in the cytoplasm before final processing in the mitochondrion combines iron and protoporphyrin IX to from heme.

Other pathological events alter iron metabolism in ways that were less easily explained. Chronic inflammation substantially lowers gastrointestinal iron absorption. At the same time, iron accumulates in fixed tissue macrophages such as those in the liver and spleen. One line of thought held that these changes lower the availability of iron thereby assisting in host defense against infection. Bacteria do require iron for proliferation. Furthermore, iron-free transferrin added to growth media inhibits bacterial growth, presumably because the protein tightly binds iron thereby making the mineral unavailable to bacteria in culture (20). The fact that preloading iron onto transferrin abrogates the bacteriostatic effect supported the idea that transferrin suppresses bacterial growth by denying iron to the organisms.

The discovery of hepcidin brought welcomed order to a confusing area (21,22). Hepatocytes secrete the small peptide hormone whose size in the plasma depends on processing of the initially synthesized 84 amino acid prepropeptide. The dominant peptides are 20 and 25 amino acids in length. The four disulfide bridges and eight cysteines in hepcidin greatly influence the structure of the molecule, which is conserved across species (23).

Hepcidin lowers the rate at which gastrointestinal enterocytes absorb iron from the gut (24). The hormone simultaneously retards iron release from fixed tissue macrophages (also called reticuloendothelial cells) consequently increasing iron content in these cells. The precise mechanism by which hepcidin signals to and alters the metabolism of these cells is unknown. Also unknown are the mechanisms that control hepcidin gene expression. The one clear fact is that the message encoding hepcidin has no IRE, meaning that the IRP/IRE control mechanism does not apply.

Table 9.2 shows changes in hepatic synthesis of hepcidin associated with a number of metabolic perturbations. Iron deficiency reduces hepcidin production and increases gastrointestinal iron absorption, which would help rebuild body iron stores. In contrast, secondary iron overload increases hepatic synthesis of hepcidin with an associated fall in iron absorption. Hypoxia lowers hepcidin production by the liver and boosts the rate of iron absorption. These results are gratifyingly consistent with clinical and experimental observations in patients.

Inflammation increases hepatic hepcidin production and lowers iron absorption. The iron content of reticuloendothelial cells increases due to dampened iron egress from stores within these cells. The idea that these changes provide a defense against bacteria is endorsed by another aspect of hepcidin physiology. Hepcidin is one of a family of small peptides with intrinsic bacteriocidal activity (25). The discovery of the molecule occurred simultaneously by one group of investigators studying iron metabolism and

TABLE 9.2
HEPCIDIN AND IRON HOMEOSTASIS

Condition	Hepcidin	Iron Absorption	RE Cell iron Content	RE Cell Iron Release
Iron deficiency	⇓	⇑	⇓	⇑
2° Iron overload	⇑	⇓	⇔	⇓
Inflammation	⇑	⇓	⇑	⇓
Hypoxia	⇓	⇑	⇓	⇑
Hereditary hemochromatosis	⇓	?	⇔	?

another investigating bacteriocidal peptides. Hepcidin expression alters iron metabolism in a fashion that would complement its bacteriocidal properties.

Derangements in iron metabolism produced by impaired hepcidin function reinforce the key role of the hormone in iron homeostasis. High plasma levels of hepcidin in transgenic mice with tonic expression of the gene produce a lethal condition in which the pups die within days of birth from severe iron deficiency (26). The high circulating hepcidin level shuts down iron absorption and apparently overrides any signals that might compensate for the severe iron deficit. In contrast, disruption of hepcidin function in other transgenic mice produces severe iron overload due to unrestrained iron absorption from the gut. Case reports exist of humans with severe iron loading syndromes where the defect correlates with an impaired hepcidin gene (27).

The iron overload condition in these patients differs from classic hereditary hemochromatosis where iron overload correlates with a defect in the gene encoding the HFE protein (28). HFE is a member of the major histocompatibility family of proteins. The molecule associates with beta-2-microglobulin to form a complex that interacts with the transferrin receptor. The transferrin receptor in this terniary protein complex can bind transferrin and mediate cellular iron uptake. However, the associated HFE/beta-2-microglobulin dampens transferrin receptor activity and consequently reduces cellular iron uptake. Enterocytes in the duodenum prominently express HFE/beta-2-microglobulin.

Hereditary hemochromatosis derives from one of several known mutations in the HFE gene, the most prominent of which replaces a cysteine with tyrosine at position 282 (29). The mutation impairs the association between HFE and beta-2-microglobulin with a resulting loss of HFE protein due to intracellular degradation. The result is transferrin receptor activity is higher than normal since less of the inhibiting HFE/beta-2-microglobulin complex is present to modulate receptor action.

Table 9.2 shows that hepcidin expression is lower than normal in hereditary hemochromatosis. This holds both for the natural disorder in humans as well as mice genetically engineered to express defective HFE and thus mimic the human condition. Hepatic iron loading in both cases should raise hepcidin expression, given the working paradigm for hepcidin control. Elevated hepatic expression of hepcidin clearly occurs with secondary iron overload in which mice receive large quantities of orally administered iron. No cogent explanation for the discrepancy exists. Both HFE and hepcidin globally affect body iron stores and metabolism. Interactions that confound the current model could exist between the two iron regulatory systems that have not yet come to light.

IRON DEFICIENCY

Iron utilization in the body is a closed circuit with extremely efficient salvage of the element from senescent cells, most prominently erythrocytes. Absorption of iron from the gastrointestinal tract precisely balances the one to two milligram obligate daily loss of the mineral. In addition, adult males have unutilized storage iron that averages three to four grams while the comparable figure for adult females is one to two grams. A negative daily iron balance for any reason draws down those stores before frank evidence of iron deficiency appears. Iron deficiency has several stages of clinical manifestation:

1. Prelatent iron deficiency occurs when stores are depleted without a change in hematocrit or serum iron levels. This stage is rarely detected.
2. Latent iron deficiency occurs when the serum iron drops and the TIBC (total iron binding capacity) increases without a change in hematocrit. A routine check of transferrin saturation occasionally uncovers this condition.
3. Overt iron deficiency anemia evokes erythrocyte microcytosis and hypochromia in addition to anemia.

The microcytic, hypochromic anemia impairs tissue oxygen delivery, producing weakness, fatigue, palpitations, and lightheadedness. The microcytosis seen with thalassemia trait can be confused with iron deficiency. Iron deficiency produces small cells with a broad range of sizes (30). Some cells are almost normal in size while others are miniscule reflecting the variable availability of iron to normoblasts during maturation. The result is a higher than normal RDW (reticulocyte distribution width). All electronic cell counters provide the RDW as a standard part of the readout. In contrast, thalassemia trait affects all cells equally, producing uniformly small cells whose size distribution and RDW are normal (31). The RDW value therefore provides valuable information that helps the clinician distinguish iron deficiency from thalassemia (32).

The plasma membranes of iron deficient red cells are abnormally rigid (33). This inflexibility could contribute to poikilocytic changes seen particularly with severe iron deficiency. These small, stiff, misshapen cells are cleared by the reticuloendothelial system, contributing to the low grade hemolysis that often accompanies iron deficiency. The basis of this alteration in erythrocyte membrane fluidity is unknown.

Causes of Iron Deficiency

With rare and esoteric exception, iron deficiency reflects either inadequate dietary intake of the mineral or blood loss. Table 9.3 outlines the major causes of inadequate iron intake. The processes listed are easy to understand in the context of the information now known about iron absorption. Dietary chelators such as the phytates in wheat or the tannins in tea tightly bind the element making it unavailable to DMT1 and the other components responsible for bringing iron into the enterocyte from the gastrointestinal lumen (34). Poor gastric acidification due, for instance, to the action of histamine H-2 blockers leaves inorganic dietary iron as insoluble and poorly absorbed ferric polyhydroxides. Metal ions such as lead, cobalt, zinc, and manganese compete directly with iron for the DMT1 uptake mechanism.

Ascorbate is an interesting and important modulator of gastrointestinal iron absorption. Physiologists have known for some time that ascorbate enhances intestinal iron absorption (35). This effect is due partly to the weak iron chelation properties of the molecule. The vitamin maintains iron in solution even when the ambient pH is relatively high. However, ascorbate is sufficiently weak in its chelation properties that iron is available to the iron uptake machinery. The cloning of Dcytb showed that this important protein has a binding site for ascorbate. The current assumption is that ascorbate bound to Dcytb performs its well known electron donor function in the conversion of Fe^{3+} to Fe^{2+} mediated by Dcytb at the interface between the enterocyte and the gastrointestinal lumen (Fig. 9.3). These data involving Dcytb fit well with earlier observations indicating that ascorbate enhances iron absorption by a means independent of changes in iron solubility (36).

TABLE 9.3
INADEQUATE IRON INTAKE

Poor Bioavailability	Iron chelators in the diet ■ Phytates ■ Tannins Failure of gastric acidification ■ Histamine H-2 antagonists ■ Vagotomy ■ Gastrectomy ■ Pernicious anemia
Inhibitors of Iron Absorption	Lead, cobalt, zinc, manganese
Loss of Absorption Surface	Pathological disruption of the GI tract ■ Celiac disease ■ Crohn's disease Bowel resection

Cryptic blood loss of sufficient magnitude to produce iron deficiency anemia occurs exclusively in the gastrointestinal tract (Table 9.4). Bleeding into the genitourinary tract can produce anemia. However, the both visible and alarming nature of urinary blood loss sends most people for evaluation early in the course of the pathology.

Bleeding into the lungs can also produce iron deficiency with anemia. Fixed tissue macrophages sequester iron from blood that escapes into the lungs and is not expectorated. This iron is outside the normal reutilization pathway shown in Figure 9.2. The material accumulates in the lungs, producing a condition called pulmonary hemosiderosis. Bronchiectasis due to chronic infection, such as tuberculosis,

TABLE 9.4
IRON LOSS BY BLEEDING

Structural Defects of the GI Tract	■ Peptic ulcer disease ■ GI malignancy ■ Bleeding varices ■ Colonic angiodysplasia ■ Meckel's diverticulum ■ Hereditary hemorrhagic telangectasia
Blood Loss via the Reproductive System	■ Menstruation ■ Pregnancy ■ Dysfunctional uterine bleeding
Intestinal Parasites	■ Hookworm ■ Whipworm

once was a common cause of pulmonary hemosiderosis. Idiopathic pulmonary hemosiderosis is a grave condition that occurs most commonly in children. The other serious clinical problems that accompany these conditions dwarf issues of iron loss and anemia, however.

Menstruation involves physiological blood loss. The gastrointestinal iron absorption machinery ramps up its activity to compensate for the higher overall iron demand. Balanced diets that include sources of well-absorbed iron, such as meat protein, allow the uptake machinery to compensate fully for the higher iron demand. Many women unfortunately have diets that provide a barely adequate amount of absorbable iron. Consequently, iron deficiency and iron deficiency anemia are common in females of reproductive age. Iron deficiency is even more common in multiparous women since each pregnancy produces a net iron deficit for the mother that approaches 1,000 milligrams. Dietary iron supplementation mitigates the effect of these losses and improves the health of reproductive age women.

The gastrointestinal tract is the Goliath of iron loss, however. Bleeding into the stomach and upper jejunum, the sites of most peptic ulcer disease, is associated with a long transit time until exit from the gastrointestinal tract. Oxidation of heme over this period produces a brownish pigment that visibly blends in with feces and often is overlooked by the patient. Colonic bleeding in contrast tends to produce bright red blood. Even here, feces can disguise relatively large quantities of blood. The specter of gastrointestinal cancer lingers over every adult with unexplained iron deficiency anemia. The clinical approach to the problem is most complex in women of reproductive age or early after menopause. A plausible explanation for iron deficiency exists, but does not exorcise the malignancy demon, since women develop gastrointestinal cancers as often as do men.

The world's leading cause of gastrointestinal blood loss is parasitic infestation. Hookworm infection, caused primarily by *Necator americanus* or *Ancylostoma duodenale*, is endemic to much of the world and often is asymptomatic (37,38). Microscopic blood loss produces significant iron deficiency, most commonly in children (39–41). Severe persistent anemia in some children causes bony changes reminiscent of thalassemia major, including frontal bossing and maxillary prominence. Over one billion people, most in tropical or subtropical areas, are infested with parasites (42). Daily blood losses exceed 11 million liters. The larvae spawn in moist soil and penetrate the skin of unprotected feet. Hookworm infection, once prevalent in the southeastern United States, declined precipitously with better sanitation and the routine use of footwear out-of-doors. Treatment programs to reduce worm infestation in children substantially lower the incidence and severity of iron deficiency (43,44).

Trichuris trichiura, the culprit in trichuriasis or whipworm infection, is believed to infest the colon of 600 to 700 million people. Only about 10% to 15% of these people have worm burdens sufficiently great to produce clinically apparent disease. *Trichuris trichiura* infestation produces less pronounced gastrointestinal bleeding than does hookworm. The organism produces iron deficiency most commonly in children between the ages of 2 and 10 years. Heavy infestations in these youngsters retard overall growth and development in addition to producing iron deficiency (45). Trichuriasis is the most common helmuthic infection encountered in Americans returning from visits to tropical or subtropical regions of the world.

Laboratory Manifestations of Iron Deficiency

Peripheral Blood Smear

Iron deficiency produces microcytic, hypochromic red cells. Central pallor can encompass 90% of the cell diameter, leaving only a small rim of hemoglobin hugging the edges of the cell. Severe iron deficiency also produces a cohort of extremely small erythrocytes that appear almost to be cell fragments. Many of these cells are irregularly shaped and have contours that resemble schistocytes.

The diameter of erythrocytes relative to lymphocyte nuclei provides the best visual estimate of red cell size. The diameter of normal red cells roughly equals that of lymphocyte nuclei. Red cells generated in an iron deficient environment often are smaller than lymphocyte nuclei and sometimes substantially so. Target cells can also occur in iron deficiency. While the finding is less common than in thalassemia, the number of target cells cannot be used to distinguish iron deficiency from thalassemia.

Iron deficiency frequently produces thrombocytosis. The high number of platelets can be visually striking and supports iron deficiency as a diagnosis. The platelets are normal in size and shape, lacking abnormalities such as the giant size seen in some hematological disorders.

Laboratory Tests

Iron deficiency substantially depresses the mean corpuscular volume (MCV). The MCV usually is lower than 80 femtoliters (fl) and values sometimes reach the mid-sixties. Red cell size varies markedly with iron deficiency making an elevated RDW virtually universal. Iron deficiency depresses both the mean corpuscular hemoglobin (MCH) and the mean corpuscular hemoglobin concentration (MCHC). The cell size and the mean cell hemoglobin define the MCHC. The MCHC is low because iron deficiency suppresses cellular hemoglobin content more profoundly than it reduces cell size. A proportional reduction in cell size and hemoglobin content would produce small

erythrocytes with a normal mean corpuscular hemoglobin concentration.

Thrombocytosis commonly produces platelet counts in the range of 600,000 to 700,000 cells per μL. Careful laboratory investigations disproved the hypothesis that thrombocytosis with iron deficiency reflects megakaryocyte activation by erythropoietin due to cross-reactivity with the structurally similar thrombopoietin (46,47). Values rarely exceed 1,000,000 cells per μL due solely to iron deficiency. A concomitant disorder should be considered in cases with extraordinarily high platelet counts.

New assay tools for iron deficiency have joined the older assessment techniques that remain in widespread use. The three stalwarts in the assessment of iron status are the serum iron, total iron binding capacity (TIBC), and serum ferritin level.

The serum iron level normally ranges between 50 and 150 mg per dL, all bound to transferrin. The TIBC expresses the maximum quantity of iron that serum transferrin can bind. This value normally ranges between 250 and 375 mg per dL. The broad range of normal values for both the serum iron and the TIBC diminishes the utility of isolated values for either parameter. These tests instead are best used to determine the transferrin saturation, which is the ratio of the serum iron to the TIBC. The transferrin saturation usually ranges between 20% and 50%. Adult males have higher normal values than do females. With severe iron deficiency the transferrin saturation often falls to below 10%.

Some laboratories measure the quantity of transferrin protein in the serum and report results in milligrams of protein per deciliter of serum. Health care providers sometimes assume incorrectly that the serum transferrin value is the same as the TIBC. The two are related but not synonymous. Transferrin is the sole plasma protein that binds iron. The TIBC therefore depends on the quantity of transferrin in the plasma. A mathematical conversion is needed to directly connect the two, however.

Each transferrin molecule binds two iron atoms. Transferrin's molecular weight and its serum mass content determine its molar content in the serum. The serum can accommodate a molar content of iron double that of transferrin. The molar iron binding capacity of the serum can be converted to a mass value using the molecular weight of iron. This mass value is the TIBC. The key point to remember is not how to perform this conversion. Rather, one should recognize the need to obtain the actual TIBC rather than the serum transferrin value when determining transferrin saturation.

The serum ferritin value expressed in nanograms of protein per milliliter is proportional to body iron stores. Normal values range between 10 and 200 nanograms per mL for reproductive age women and 15 and 400 nanograms per mL for men (48). Ethnic and racial variations in serum ferritin levels likely represent population trends in body iron stores (49). Serum ferritin levels in postmenopausal women approximate those of their male counterparts. The serum ferritin value alone often can be used to estimate the iron status of a patient.

A common point of confusion regarding the relationship of serum ferritin and serum iron arises from the fact that ferritin is the storehouse for intracellular iron (50). A widespread misconception is that serum ferritin is the same as intracellular ferritin and consequently transports iron in the serum. In fact, serum ferritin is a secreted protein that contains essentially no iron (51). Cellular iron stores modulate the secretion of this virtually iron-free form of ferritin. Consequently, serum ferritin is merely a surrogate marker of body iron stores (52).

Comorbid conditions sometimes conspire to obscure the diagnosis of iron deficiency as determined either by transferrin saturation or serum ferritin values. The most important of these is chronic inflammation. Ferritin is an acute phase protein whose levels rise as a part of the inflammatory response (53). Cytokines such as interleukin-6 and tumor necrosis factor produced with inflammation enhance ferritin synthesis and secretion (54). Baseline ferritin values are high in patients with inflammatory disorders irrespective of body iron stores meaning that ferritin cannot be used to assay iron deficiency. Some investigators have combined the assessment of serum ferritin levels with an assay of C-reactive protein and found a good correlation with iron stores determined by bone marrow aspiration and iron staining (55).

Serum transferrin levels also rise with inflammation while the serum iron value tends to fall reflecting the aforementioned action of hepcidin. For a given level of body iron stores, the transferrin saturation with inflammation is lower than expected. Chronic inflammation therefore severely compromises the quality of information gained from the two tests most commonly used in the noninvasive assessment of iron stores.

One test that provides information on iron status independently of serum ferritin or transferrin saturation values is the soluble transferrin receptor assay (56). The transferrin receptor is an intrinsic membrane protein, meaning that it is anchored securely in the plasma membrane bilayer (57). Proteases can clip the receptor protein just above its membrane insertion point, releasing a soluble fragment of the receptor into the circulation (58,59).

The initial reports of soluble transferrin receptors in the circulation were met with skepticism. Subsequent studies not only bore out these early observations but also showed that iron deficiency elevates the quantity of circulating transferrin receptor (60,61). These data suggested that the soluble transferrin receptor assay might be a valuable tool

in the assessment of body iron stores (62). Importantly, chronic inflammation does not alter the soluble transferrin receptor level (63,64).

Some important caveats exist with respect to the soluble transferrin receptor assay and body iron stores. First, the soluble transferrin receptor level increases markedly with hemolytic anemias and with ineffective erythropoiesis. The soluble transferrin receptor level is high in patients with sickle cell disease as well as those with thalassemia (65,66). Erythroid cells in the bone marrow account for most transferrin receptors in the body and are the source of most soluble transferrin receptor in the serum. The rise in the number of erythroid precursors with hemolytic anemias boosts the quantity of soluble transferrin receptor (67). The greater number of erythroid precursors associated with ineffective erythropoiesis also increases the quantity of soluble transferrin receptors (68).

A second issue with the soluble transferrin receptor assay involves standardization. A number of commercial kits are available for this ELISA-based technique. Kits from different manufacturers can give different results when used to assay a single blood sample. The variability likely reflects factors such as differences in antibody affinity for the transferrin receptor and the technical approaches recommended for different kits. No standard exists, which limits comparisons between laboratories and investigators. Rigorous in-house testing and standardization is essential for any institution that uses the soluble transferrin receptor assay.

A mathematical transformation of the data from the soluble transferrin receptor assay can improve its correlation with iron deficiency. Plotting the soluble transferrin receptor value against the log of the serum ferritin value produces a parameter (the soluble transferrin receptor index) that correlates well with patient iron status as determined by other means (69). This approach is most important in patients with the chronic inflammation who might also have iron deficiency (70). The soluble transferrin receptor assay unfortunately has not solved completely the difficulty of detecting iron deficiency during pregnancy (71). Empirical treatment to prevent iron deficiency remains the best approach in pregnant women.

Another test that sometimes provides insight into the iron status in murky situations is the zinc protoporphyrin (ZPP) level (72). The fluorescent nature of zinc protoporphyrin makes its detection easy in erythrocytes derived from iron deficient normoblasts (73). Accumulation of zinc protoporphyrin in erythrocytes is not exclusive to iron deficiency, however. Drugs that interfere with ferrochelatase function, such as isoniazid, also produce ZPP laden red cells. Lead or aluminum intoxication likewise markedly raise erythrocyte ZPP levels due to their interference with cellular iron metabolism (74). The assay is in fact a common screening tool for lead poisoning (75). The ZPP test as applied to iron deficiency usually provides value clues but might not be definitive.

Bone marrow aspiration with Prussian blue staining for iron is the gold standard in the assessment of iron deficiency. Microscopic examination of developing normoblasts usually reveals one or two iron granules per cell. These granules are absent in iron deficiency. Iron deficient normoblasts are also morphologically irregular with ragged appearing edges. Bone marrow reticuloendothelial cells usually contain some iron reflecting the removal of the few aberrant red cells that always arise with erythropoiesis. With significant iron deficiency, the reticuloendothelial cells lack iron as the mineral is quickly cycled back into erythropoiesis. Bone marrow reticuloendothelial cells lacking iron makes the diagnosis of iron deficiency. The procedure requires a hematologist or oncologist and unfortunately is not readily available in all clinical settings.

FUNCTIONAL IRON DEFICIENCY

Recombinant human erythropoietin (rHuEPO) was one of the first clinically useful agents produced by recombinant DNA technology. Used to correct the anemia of end-stage renal disease (ESRD), this hormone provided new insight into the kinetic relationship between iron and erythropoietin in red cell production. Erythropoietin treatment of anemia in patients with ESRD also underscored the variable nature of storage iron. The shifting states of storage iron contribute to the inconsistency with which erythropoietin corrects the anemia of renal failure (76).

With steady-state erythropoiesis, iron and erythropoietin each flow to the bone marrow at constant, low rates. Patients with ESRD receive recombinant human erythropoietin in intermittent surges, either as intravenous boluses or subcutaneous depot injections. The resulting kinetics of erythropoiesis are markedly aberrant and strain the production process. Erythropoietin, the accelerator of erythroid proliferation is not coordinated with the supply of iron, the fuel for hemoglobin production (Fig. 9.5). This imbalance almost never occurs naturally. The rHuEPO jars previously quiescent cells to proliferate and produce hemoglobin. The requirement for iron jumps dramatically, and outstrips iron delivery by transferrin.

Interplay Between Iron and Erythropoietin

Erythropoietin prompts proliferation and differentiation of erythroid precursors, with an upsurge in heme synthesis (77). Iron is taken into the cells from transferrin by cell surface transferrin receptors, transported to the mitochondria, and inserted into the protoporphyrin IX ring by ferrochelatase. The newly synthesized heme modulates globin

synthesis in part through its effect on the translational factor, eIF-2. Primitive erythroid cells have relatively few transferrin receptors (78). The number increases with differentiation, peaking at over 10^6 per cell in the late pronormoblasts. The number subsequently declines, to the point that mature erythroid cells lack transferrin receptors altogether. This variable expression of transferrin receptors means that iron delivery must be synchronized both with proliferation and stage of erythroid development. Late normoblasts, for instance, cannot compensate for iron that was not delivered earlier to basophilic normoblasts. These late cells have fewer transferrin receptors, and those receptors are busy supplying iron for currently produced heme molecules.

Even with normal body iron stores and normal transferrin saturation, robust proliferation of erythroid precursors can create a demand that outstrips the capacity of the iron delivery system (79,80). Transferrin iron saturation falls as the available iron on plasma transferrin is stripped off by voracious erythroid precursors (81). Plasma iron turnover (PIT) rises, as does erythron iron turnover (EIT) and erythron transferrin uptake (ETU). The late arrival of newly mobilized storage iron fails to prevent production of hypochromic cells. This is iron-erythropoietin kinetic imbalance or *functional iron deficiency* (82,83).

Erythropoietin speeds maturation and development of the BFU-e and CFU-e erythroid precursors (84) to the proerythroblast stage. As shown in Figure 9.6, iron influx into the cells via the transferrin receptor is needed for hemoglobin synthesis. If the cells move through maturation and development faster than transferrin can provide iron, they end up as hypochromic cells with hemoglobin levels that are lower than normal.

Patients with ESRD who received erythropoietin when the drug was initially introduced had substantial iron stores from their earlier chronic transfusions. In fact, death from iron overload was a significant concern for dialysis patients. The enormous quantity of storage iron in these patients produced circulating transferrin with supraphysiological quantities of bound iron (i.e., transferrin saturations of 70% to 90%). As a result, the available transferrin-bound iron could match the bursts of heme production induced by pharmacological levels of exogenously administered rHuEPO.

In these patients, the proliferative capacity of the erythroid precursors was the rate-limiting factor in erythrocyte production. The number of precursor cells and the quantity of erythropoietin they encountered determined the number of red cells generated. Iron mobilization and red cell production were so efficient in these early patients that rHuEPO treatment combined with phlebotomy was sometimes used to remove excess iron (85).

Patients with ordinary iron stores treated with erythropoietin had a completely different experience. Here, the cells were jolted into accelerated proliferation in the face of transferrin saturations ranging only between 30% and 50%. Iron was rapidly pulled into the developing erythroid cells. In some instances, transferrin-bound iron could sustain maximal synthesis of hemoglobin. In other cases, however, iron availability was suboptimal, producing functional iron deficiency. Even though red cell production increased substantially, the transferrin saturation fell, reflecting the strain on the supply system (86). The quantity of storage iron was more than adequate to meet the demands of hemoglobin synthesis, but could not be mobilized onto transferrin with sufficient speed to satisfy the developing normoblasts. The kinetic mismatch in circulating rHuEPO and circulating iron-loaded transferrin is the key to functional iron deficiency (87).

New erythroid cells in the form of reticulocytes emerge from the bone marrow within three days of the activation of BFU-e and CFU-e precursors by exogenous rHepo. A number of advanced blood cell analyzers can estimate the hemoglobin content of reticulocytes. Hypochromic reticulocytes are the sine qua non of functional iron deficiency. These cells arise from bone marrow normoblasts that experience a mismatch between rHuEPO and iron-loaded transferrin during development (88,89). This information has its greatest use in determining whether patients on dialysis require supplemental iron for optimal production of red cells (90,91). The standard parameters such as serum ferritin and transferrin saturation often are normal. rHuEPO administration produces hypochromic reticulocytes however, indicating a need for supplemental iron to balance hemoglobin synthesis (92). The reticulocyte hemoglobin determination permits optimal use of rHuEPO, which improves care and saves money.

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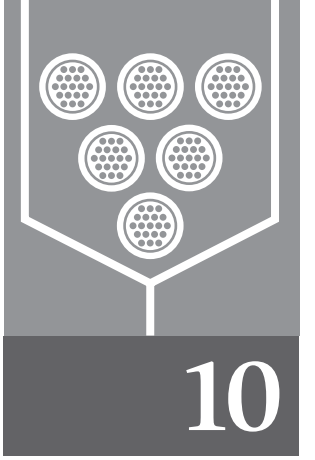

New Concepts in Oxygen Transport

10

Aryeh Shander *Tanuja S. Rijhwani* *Nimish Nemani* *Carmine Gianatiempo*

Hemoglobin is an essential component of the circulatory system of humans and one of its main physiological functions is to transport oxygen from the lungs to the tissues and buffer with carbon dioxide elimination. Normal human hemoglobin (HbA) is one of the most studied proteins. In the late 1950s, Max Perutz and his colleagues at Cambridge University were the first to determine the three dimensional structure of hemoglobin. Normal adult hemoglobin is composed of four subunits of heme, two alpha and two beta chains. Heme is a ringlike structure with a central iron atom that binds to an oxygen atom. Oxygen is poorly soluble in water and plasma. Hemoglobin, the respiratory pigment, is packed in red blood cells and thus protected from the oxidative stresses of the environment. Hemoglobin structure is known for both its deoxygenated state, when it has no oxygen, and its oxygenated form carrying a full load of four oxygen atoms. Partially oxygenated hemoglobin becomes fully oxygenated with increasing partial pressures of oxygen.

The four basic and important steps in oxygen transport constitute flow of oxygen from our environment into the lungs; diffusion into the blood; oxygen flow to the various tissues of the body; and diffusion into the mitochondria of the cell.

PATHOPHYSIOLOGY OF OXYGEN DEPRIVATION

Reduced oxygen delivery may arise from the following:

- Decreased partial pressure of oxygen, as at high altitude.
- Impaired diffusion across the lung–blood interface.
- Reduced cardiac output.
- Impaired diffusion across the blood–tissue interface.

Events Occurring at the Circulatory Level

In the event of acute blood loss, the body compensates through a variety of feedback mechanisms. A combination of the actions of baroreceptor reflexes, the central nervous system ischemic response, reverse stress–relaxation of the circulatory system, as well as the release of angiotensin and vasopressin, and redistribution of extracellular fluid to the intravascular space, are responsible for the initial maintenance of life-sustaining circulation (1). Sympathetic reflexes through the release of catecholamines become maximally activated within 30 seconds of the hemorrhagic insult (1). Blood pressure is maintained at the expense of impaired blood flow to most tissues except the brain and the heart. The cerebral and coronary vessels do not constrict significantly and are well preserved despite systemic hypoperfusion. When compensatory mechanisms are overwhelmed, autoregulation fails to the point that blood flow to all the tissues can be impaired resulting in cellular metabolic dysfunction and finally shock (1).

Events Occurring at the Cellular Level

Essential cellular processes, such as membrane transport, protein synthesis, and mechanical work, are driven by the energy stored in high-energy phosphate bonds of adenosine triphosphate (ATP) (1). ATP, in turn, is generated by the interaction of carbohydrate, protein, and lipid substrates with oxygen. Glucose entering cells is converted to

pyruvate through a series of steps known as glycolysis. Pyruvate then enters the tricarboxylic acid (TCA) cycle where the oxidation of hydrogen ions releases large amount of ATP.

When blood flow and/or oxygen content are limited, intracellular oxygen tensions may fall below the critical value (<1 mmHg), resulting in decreased oxygen utilization and a fall in ATP production—the metabolic expenditure thus gets reprioritized.

Various adaptive mechanisms aimed at restricting ATP consumption to life-sustaining processes are promoted as a result of diminished oxygen tensions. Such adaptive mechanisms are mediated in part by the transcriptional and posttranscriptional effects of molecules, such as hypoxia-inducible factor (HIF)-1 (2). During hypoxic conditions, components of HIF-1 are activated and stabilized. This in turn, recognizes a DNA sequence (hypoxia response element) located in the promoter regions of downstream hypoxia responsive genes. Increased expressor genes related to erythropoietin production have been shown to be related to HIF-1 activity. The vascular system underlies tight oxygen-regulated control by hypoxia inducible factors such as vascular endothelial growth factor (VEGF). The induction of angiogenesis by VEGF leads to an increase in the vascular density and hence a decrease in the oxygen diffusion distance. However, local blood flow under pathophysiological conditions is controlled by modulation of the vascular tone through production of nitric oxide, NO (via the action of inducible nitric oxide synthase), CO (via heme oxygenase-1 activation), endothelin 1, adrenomedullin, or activation of the α_{1B}-adrenergic receptor, all of which involve HIF-1 target genes, too (3–6). The effects of hypoxia- HIF-1 transcription may protect cells during hypoxic conditions. It has been postulated that inflammatory mediators can adversely affect these interactions. It follows that tissues subjected to low oxygen delivery during critical illness may be at profound risk of the damaging effects of hypoxemia (7).

The consequences of severe blood flow limitation on intracellular oxygen utilization are varied. Myocyte dysfunction leads to impaired cardiac output and ultimately to cardiogenic shock. Endothelial and epithelial hypoxia can cause increased permeability and progressive edema. This extracellular accumulation of fluid can perhaps induce translocation of bacteria or toxins from the gut. The natural progression of the pathophysiologic cascade resulting from cellular hypoxia is cellular dysfunction, cell death, and multiple organ failure (8).

The resuscitation efforts themselves can be damaging as reperfusion of ischemic tissue beds could force local inflammatory mediators into the systemic circulation. These local inflammatory mediators are notorious and result in oxygen-radical mediated injury, worsened interstitial edema, and/or increased metabolic demands on organs with already depleted functional reserves.

Hemoglobin and the Paracrine and Endocrine Functions of Nitric Oxide

In the microcirculation (the circulation of the blood through the microvascular network lying between the arterioles and venules, which includes capillaries, metarterioles, and arteriovenous anastomoses; and the flow of blood through this network), blood flow is regulated by physiological oxygen gradients. The progressive decrease in the oxygen content of blood as the diameter of the arteriolar blood vessels decreases is coupled with graded vasodilation. A decrease in the oxygen content of blood in response to, for example, increased muscle activity, stimulates an increase in blood flow. When the demand for oxygen is reduced, the oxygen content of the blood rises and blood flow decreases. Thus, blood flow is matched to the metabolic requirements (i.e., tissue consumption). The detailed biochemical mechanism by which this occurs remains unknown (9).

Nitric oxide, NO, produced by endothelial cells also diffuses into the flowing blood, where it reacts with molecules in the plasma and especially oxyhemoglobin in erythrocytes and is rapidly destroyed. This reaction, which produces methemoglobin and nitrate ions, accounts for the deleterious effects of blood substitutes based on free hemoglobin, which efficiently scavenge nitric oxide (10). Since nitric oxide is rapidly destroyed by hemoglobin, questions are raised as to whether it is a paracrine agent with only local effects or if it is disseminated throughout the body like a hormone (10). Nitric oxide is not completely destroyed by its reaction with hemoglobin, but also reacts with the heme groups of deoxyhemoglobin to form S-nitrosohemoglobin (10).

In a series of studies (11–13) and in a recently published report (9), Stamler and his colleagues suggested that S-nitrosohemoglobin is a source of bioactive nitric oxide and a crucial component of the cardiorespiratory cycle. They propose that at physiological concentrations, NO reacts preferentially with the beta subunits of hemoglobin, forming S-nitrosohemoglobin in the oxygenated state. On the other hand, at supraphysiologic levels (for example, in septic shock), NO tends to react with the alpha subunits and favors the deoxygenated state. The disposition and reactivity of NO bound to hemoglobin is therefore a function of various variables such as other allosteric factors affecting hemoglobin (pH; partial pressure of carbon dioxide, pCO_2; partial pressure of O_2, pO_2) and the ratio of their concentrations to heme.

DIAGNOSIS OF IMPAIRED OXYGEN DELIVERY

Clinical and Biochemical Indicators of Shock

Some of the more unreliable clinical indices of shock are pulse, blood pressure, skin temperature, and urine output. These indices are notoriously slow to change in the presence of compensatory mechanisms and abnormal values occur only in the late stages of hypoperfusion. Hemodynamic parameters such as pulmonary capillary wedge pressures (PCWP) and cardiac output are prone to misinterpretation (2).

Impaired oxygen delivery results in abnormalities in pyruvate metabolism with the subsequent accumulation of lactic acid. Base deficit, serum lactate, anion gap, and pH are used as measures of the degree of acidemia and the magnitude of shock. These are global measures and are not sensitive indicators of regional hypoperfusion (14,15).

Measurements of Adequacy of Systemic Oxygen Delivery

In healthy subjects, resting oxygen delivery (DO2) is approximately 1000 mL/per min, and approximately 250 ml per min of this oxygen is required for tissue metabolic process (VO2), so that usual oxygen extraction is 25%. If oxygen delivery decreases, oxygen extraction by the tissues increases, so that oxygen consumption remains relatively constant (16). The efficiency of extraction varies from tissue to tissue; the myocardium for example, extracts close to 50% to 90% of its delivered oxygen. Oxygen consumption begins to decrease below a critical threshold of oxygen delivery (approximately 5 mL/kg/min in human) (17,18). Below this point, any decrease in oxygen delivery is associated with a decrease in oxygen consumption and is therefore said to be supply dependent (DO_2crit) (16). Below the DO_2crit threshold, oxygen delivery impairment is thought to correspond to progressive cellular functional impairment; therefore, all therapeutic efforts are aimed at preventing this supply dependency (16).

Diagnostic Implications of Regional Hypoperfusion in Shock

Redistribution of blood flow to vital tissue beds and away from capillaries supplying the less critical organs is the basic circulatory response to hypovolemic shock. As a result of this redistribution, blood flow to the splanchnic organs may be disproportionately reduced in response to hypovolemia, and a measurement of this phenomenon may provide a more sensitive indication of impairment of DO_2 than the global measures described earlier.

Splanchnic ischemia may contribute to the progression of multiple organ failure by leading to a reduction in gut barrier function and translocation of endotoxin, inflammatory mediators, and microorganisms through an ischemic and leaky gastrointestinal mucosa (19).

GASTRIC TONOMETRY

The Rationale Behind Gastric Tonometry

Dysoxia, or oxygen debt, is supported by anaerobic metabolism that generates organic acids. Regional acidosis, however, is difficult to measure directly; carbon dioxide generated from the acid-buffering effect of bicarbonate is more readily measurable.

The gut is sensitive to ischemia; periods of hypoperfusion may cause the release of inflammatory cytokines and bacterial translocation, resulting in damage to remote organs (20). Dawson and colleagues (21) were the first to suggest the concept that fluid in a hollow viscus could be used to approximate gas tensions in surrounding tissues. In the late 1950s, Boda and Muryani (22) were able to measure gastric intramucosal PCO_2. The investigators also recognized that the gastric PCO_2 estimates of arterial PCO_2 were misleadingly high.

Fiddian-Green and colleagues (23) revived the concept of gastric tonometry in the early 1980s. Gastric tonometry has since been proposed as a simple tool for assessing regional perfusion of the gut by inserting a balloon into the stomach to measure intramucosal PCO_2. The unit of measurement employed in these studies was the gastric intramucosal pH (pHi), which was calculated by applying the measured gastric PCO_2 levels and arterial bicarbonate concentrations to a modified Henderson-Hasselbach equation:

$$pHi = 6.1 + \log 10\ [HCO3–] / 0.03 \times PCO_2.$$

Gutierrez and Brown proposed the normal value of pHi to equal 7.37 ± 0.04 (mean, SD) (23a).

These calculations were based on three assumptions (23):

1. CO_2 diffuses freely in the tissues.
2. PCO_2 in the luminal fluid is in equilibrium with the mucosal PCO_2.
3. Arterial bicarbonate concentration equals that of intestinal mucosal bicarbonate.

These assumptions underlying the calculation of pHi are valid except for conditions when partial or total ischemia

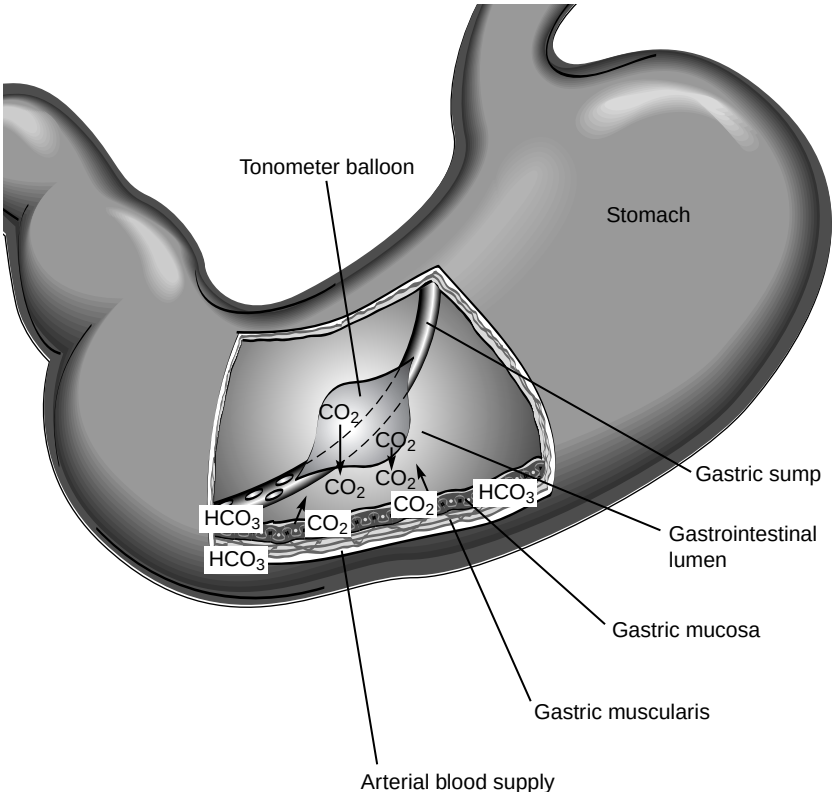

Figure 10.1 Schematic diagram of gastric tonometry. (Adapted from Heard SO. Gastric tonometry: the hemodynamic monitor of choice [Pro]. *Chest*. 2003;123 [suppl 5]:469S–474S.)

is present; the tonometer will underestimate the intestinal pHi in underperfused tissue (24).

Due to these problems with the interpretation of pHi, the difference between tonometric and arterial pCO_2 called pCO_2-gap is gaining popularity (Fig. 10.1).

Validation

Follow-up studies demonstrated a high degree of correlation between the calculated pHi and pH microelectrode-calculated mucosal pH ($R^2 = 0.79$) (23).

Clinical studies have also attempted to validate the tonometry tool by demonstrating associations between pHi measurements and patient outcomes. Gastric mucosal pH was found to be a highly sensitive predictor of complications in 85 patients after elective cardiac surgery (26).

In prospective studies by Maynard et al. (15) and Roumen et al. (27), the authors concluded that gastric mucosal pH was a reliable indicator of the adequacy of tissue oxygenation and predictor of mortality in their respective study populations.

These findings were challenged by the results of a prospective study by Boyd et al. (28). The authors suggested that the information obtained from tonometry does not improve upon that provided by the usual indicators of hypoperfusion (e.g., base deficit).

Other GI Monitoring Sites

Carbon dioxide is measureable in other tissue beds, and the principles first described for gastric tonometry have been expanded to other sites in the GI tract. The goal being that early detection of oxygen debt in the gut may help prevent multiple organ dysfunction.

Walley et al. (29) studied small bowel tonometry and concluded that compared to gastric tonometry, small bowel tonometry is noisy and inaccurate for detecting gut ischemia. Furthermore, placement of tonometers in the small bowel is more problematic than placement in the stomach.

Jacques et al. (30) studied the sigmoid colon, which is a more accessible tissue bed. The authors concluded that a wide variation in sigmoid pHi limits the value of individual pHi measurements in the detection of ischemia.

The tongue and esophagus have also been employed as sites for measuring regional perfusion (31).

Limitations of Tonometry

Several clinical trials have shown that the validity of gastric tonometry as a proxy for monitoring perfusion to the rest of the hepatosplanchnic bed is doubtful.

Creuter et al. (32) measured gastric PCO_2 gap, hepatosplanchnic blood flow, hepatic venous saturation, and hepatic venoarterial PCO_2 gradient in 36 patients with severe sepsis and found that gastric PCO_2 did not correlate with other indices of hepatosplanchnic blood flow. Similar findings have been found in cardiac surgery patients treated with dobutamine in studies by Thoren et al. (33) and Parviainen et al. (34).

Despite the limitations of gastric tonometry, this minimally invasive monitoring device remains one of the few organ-specific monitors approved for clinical use. The gastric tonometer may be of value as a prognostic tool and to detect hypovolemia before it is manifested by the appearance of global hemodynamic indices.

NEWER TECHNIQUES

Balloonless tonometry (35) and fiberoptic CO2 sensors (36–38) have been described as methods for measuring the adequacy of DO_2.

Balloonless Tonometry

Salzman et al. (35) performed a prospective, unblinded comparison of two methods of mucosal PCO_2 measurement to determine if air introduced directly into the lumen of a hollow viscus can be used instead of fluid in a Silastic balloon to estimate gastrointestinal mucosal PCO_2. The authors concluded that under stable hemodynamic and respiratory conditions, air tonometry (which, in theory, can be performed using a conventional nasogastric or nasoenteric feeding tube, i.e., balloonless) estimates gastrointestinal mucosal PCO_2 as accurately as standard saline tonometry in the stomach or ileum.

Fiberoptic CO_2 Sensors

In a prospective observational study (in a rat model) (38), subcutaneous oxygen tension (electrochemical-fiberoptic gas sensors inserted into silastic tubing placed in the subcutaneous tissue) provided similar information as ileal luminal PCO_2 and was more rapidly responsive than subcutaneous carbon dioxide tensions and arterial lactate during evolving hemorrhagic shock and resuscitation.

Venkatesh et al. (36) performed an observational study involving seven patients with major burns ($54 \pm 21\%$ total body surface area) during the first 36 hours of fluid resuscitation. Silastic tubing was placed in the subcutaneous tissue just beneath normal skin and deep partial thickness burn. Fiberoptic sensors inserted into the tubing measured subcutaneous oxygen and carbon dioxide tensions in the burnt skin (PO_2scb and PCO_2scb) and normal skin (PO_2scn and PCO_2scn) continuously. Gastric intramucosal pH (pHi) and the mucosal CO_2 (PCO_2m) gap were calculated using gastric tonometers. Mean arterial pressure, arterial pH, lactate, and pHi measurements were obtained for 36 hours.

There were no significant differences in mean arterial pressure, arterial pH, or lactate concentrations throughout the study period; whereas indices of tissue oxygenation showed deterioration. The authors concluded that despite adequate global indices of tissue perfusion after 36 hours of resuscitation, tissue monitoring indicated significant deterioration in the splanchnic circulation and in the normal and burnt skin.

Near Infrared Spectroscopy (NIRS)

Puyana et al. (39) have demonstrated that directly measured tissue pH is an early and sensitive indicator of shock and the results of resuscitation (40). Although monitoring of tissue pH in splanchnic organs is sensitive to the magnitude of hemorrhage, monitoring tissue pH of other organs may also be satisfactory for the early detection of hypoperfusion (41). Under conditions of reduced blood pressure, studies have shown that blood flow to the skeletal muscle mirrors the reduction in blood flow to the splanchnic organs (42,43); thus, skeletal muscle is a potential proxy for monitoring perfusion to the gut. The skeletal muscle is easily and rapidly accessible for the application of a noninvasive or minimally invasive probe.

Soller et al. (44) have demonstrated the ability to noninvasively measure muscle pH through the skin using NIRS.

NIRS has been utilized as a tool to determine the redox state of light absorbing molecules. This technology is based on the Beer-Lambert law, which states that light transmission through a solution with a dissolved solute decreases exponentially as the concentration of the solute increases. In mammalian tissue, only three compounds change their spectra when oxygenated: cytochrome aa_3, myoglobin, and hemoglobin. Because the absorption spectra of oxyhemoglobin and deoxyhemoglobin differs, their relative concentrations within tissue change with oxygenation; thus, the relative concentration of the type of hemoglobin can be determined (45–57). NIRS concentrations are taken without regard to systole or diastole, and because only 20% of blood is intraarterial, spectroscopic measurements are primarily indicative of venous oxyhemoglobin concentration.

The simplicity, portability, and noninvasive nature of NIRS technology could make this instrument quite valuable

in the combat casualty or prehospital setting. NIRS may facilitate our advancement in the management of the patient's oxygen delivery by providing information at the cellular level.

Various studies have demonstrated the ability to noninvasively measure muscle pH through the skin using near infrared spectroscopy (44,55). Puyana et al. (39) have shown that muscle pH correlates well with bowel and stomach pH during hemorrhagic shock in swine. Soller et al. (58) have demonstrated that muscle pH correlates well with liver pH during shock and resuscitation in a constant, low pressure swine hemorrhagic shock model and is a predictor of liver injury. In this study, the trends in muscle pH mirror the trends in liver pH during both shock and the resuscitation phase. The results of this study suggest the need for further investigations of the noninvasive pH sensors.

Cohn et al. (47) used a NIRS prototype in a porcine hemorrhage model to demonstrate that muscle tissue oxygen saturation was at least as reliable as invasive systemic oxygenation variables (such as SvO_2, arterial lactate, base excess) as an index of shock.

Irrespective of the technique used, it is becoming increasingly clear that shock as a concept is applicable at the microcirculatory level. Shock can be defined as the presence of inadequate tissue perfusion and tissue oxygenation resulting from an abnormality of the circulatory system. The detection of microvascular hypoperfusion correlates with increased mortality. Such redistribution of blood flow, if of detectable magnitude, may signal the severity of compensated shock and therefore be an indicator of impending mortality, or it may, through certain mechanisms such as translocation or liberation of cytokines, contribute to the progression of shock to multiorgan dysfunction.

Rational approaches to aggressive management of these circulatory abnormalities will depend on understanding of the factors determining regional blood flow characteristics and if those specific treatment approaches will aid in improving regional blood flow. Continued research at the cellular level will help resolve such controversies.

OXYGEN DELIVERY-BASED THERAPIES

General principles: include judicious fluid resuscitation and correction of anemia.

Systemic Oxygen Delivery-based Therapies

Early Goal-Directed Therapy

The Early Goal-Directed Therapy Collaborative Group designed an emergency department therapeutic protocol based on the rationale that augmentation of DO_2 before the establishment of cellular hypoxic damage could improve outcome in patients with the hemodynamic abnormalities associated with septic shock (59). This study is plagued by several limitations. Nevertheless, the results support the role of hypoxia in the cascade of cellular and organ deterioration that is representative of progressive shock states. Although intriguing, the results of this study should be interpreted with caution until more evidence has accumulated.

Supranormal DO_2

Bishop et al. (60) observed that patients with increased oxygen delivery to supranormal levels after severe trauma had higher survival rates than patients unable to mount such a response. These results have not been uniformly supported by others including one study from the same group, which found results to the contrary (61). A 1996 meta-analysis of seven studies by Heyland et al. (62) also concluded that interventions designed to achieve supraphysiologic values of cardiac index, DO_2, and VO_2 do not significantly reduce mortality, except maybe when initiated preoperatively.

In a meta-analysis by Kern et al. (63), incorporating studies published until 2002, grouped according to the timing of interventions, the authors concluded that early optimization of DO_2 confers a substantial survival benefit. Also, they showed that hemodynamic optimization after the onset of organ failure did not yield a substantial benefit.

In a large, well designed trial by Sandham et al. (64), no advantage was demonstrated in preoperative optimization of pulmonary artery catheter-derived hemodynamic parameters in high-risk surgical patients.

GASTRIC TONOMETRY-BASED THERAPIES

Three studies in the trauma arena have examined the role of pHi-directed shock resuscitation. In a prospective study by Roumen et al. (27), the evaluation of pHi in 15 patients found that a pHi <7.32 within 48 hours of admission was associated with increased morbidity and mortality. The authors suggested that monitoring gastric pHi is useful in severely injured patients admitted to the ICU.

In another prospective study by Chang et al. (65) involving 20 critically ill patients, the authors noted higher mortality rates in subjects with a low initial pHi that did not correct within 24 hours (50% versus 0%), as well as higher incidence of organ dysfunction. The authors concluded that splanchnic perfusion is an important factor in the pathogenesis of multiple organ failure and that gastric

tonometry as an indicator of gastric ischemia is a useful prognostic indicator in underperfused patients.

Ivatury et al. (66), in a prospective trauma trial, noticed that a persistently low pHi was frequently associated with complications such as intra-abdominal anastomotic leak, compartment syndrome, abscess formation, and others. The authors concluded that gastric mucosal pH may be an important marker for assessing the adequacy of resuscitation.

Despite extensive experience with gastric tonometry, no trial to date has documented better outcomes with tonometry-directed therapy. Additionally, there is little evidence from randomized studies that substantiates that intramucosal pH can favorably and reproducibly be influenced compared to placebo.

Gomersall et al. (66a) speculated that their failure to demonstrate a difference in outcome with tonometry-directed therapy in critically ill patients may have resulted from the inability of dobutamine to produce a significant change in pHi or that pHi is merely a surrogate marker of disease, as suggested by the gut–motor hypothesis proponents.

RATIONALE FOR DEVELOPMENT OF HEMOGLOBIN SUBSTITUTES

The currently available modalities for improving DO_2 in critically ill patients have several limitations and are associated with numerous uncertainties that have prompted investigators to look for other alternatives.

Recombinant human erythropoietin may help by augmenting red cell production in this population. Horwin et al. (67) demonstrated a 19% reduction in blood transfusion in a group of critically ill patients who received a weekly high dose of recombinant human erythropoietin compared with placebo. The observed reduction of 0.6 units per transfusion was statistically significant.

Hemoglobin-based oxygen carriers have been undergoing extensive evaluation as a potential alternative to allogeneic blood. Unfortunately, extensive research and developmental efforts to date have led to limited success with tetramerized human and bovine hemoglobin and second-generation perfluorocarbons. The current generation of artificial oxygen carriers (AOC) are designed to replace only one of the many functions of human blood transporting oxygen to the tissues. The purpose of these AOCs is to provide oxygen in the event of deficiency and thus avoid or reduce the need for transfusion of allogeneic blood (Table 10.1).

AOCs fall into two main categories: perfluorocarbon (PFC)-based substitutes and hemoglobin-based substitutes (HBOCs). HBOCs use modified human, animal, or recombinant hemoglobin. The type of hemoglobin used, and the modifications made to it, affect the results obtained (Table 10.2).

TABLE 10.1
CHARACTERISTICS OF AN IDEAL BLOOD SUBSTITUTE

- O_2 and CO_2 transport and delivery capacity equivalent to natural hemoglobin.
- Similar viscosity to blood.
- Maintains intravascular pH.
- Sufficient intravascular existence.
- Absence of renal toxicity.
- Does not overwhelm the reticuloendothelial system.
- Nonantigenic.
- Long-term storage possible.
- Cost equal to, or marginally higher than, the cost of a unit of blood (to be readily acceptable).
- Easy to use.
- Immediate availability.

(Adapted from Remy B, Deby-Dupont G, Lamy M. Red blood cell substitutes: fluorocarbon emulsions and haemoglobin solutions. *Br Med Bull*. 1999;55(1):277–298.)

Definition of Efficacy as It Relates to HBOCs

Demonstrating survival benefit as well as correlating oxygen delivery and consumption parameters with survival is difficult in clinical trials of HBOCs. Therefore, avoidance of allogeneic blood transfusion has replaced survival rate as a universal marker of efficacy for these solutions currently undergoing clinical trials.

Cost of Oxygen Carriers

Costs of oxygen carriers are still being determined. The unit cost of most of these oxygen carriers however is predicted to be higher than the cost of a unit of allogeneic blood.

Baxter's product HemAssist (Diaspirin cross-linked hemoglobin) underwent two phase III clinical trials. The first double-blind trial studied 181 perioperative patients out of a planned 400 subjects. The trial was terminated early due to two important adverse events: acute respiratory distress syndrome and multi-organ dysfunction syndrome. It is noteworthy, however, that despite these adverse events, there was a 24% reduction in the rate of transfusion in the HemAssist arm.

A second single-blind trial in trauma patients, comparing 1 L of HemAssist versus 1 L of PRBCs, was terminated prematurely after a 46% mortality rate was noted in the group that received blood substitute compared to control (71).

Perfluorochemical (PFC) emulsions (example, Fluosol-DA) initially appeared promising due to their ability to

TABLE 10.2
DEVELOPMENT PHASE AND INDICATIONS OF HB-BASED OXYGEN CARRIERS

General Description	Proprietary Name and Sponsor	Solution Hb Concentration (g/dL)	Development Phase and Indication
(DCLHb) Diaspirin cross-linked hemoglobin	HemAssist Baxter Healthcare	10	Surgery, ischemic stroke, trauma terminated
(rHb 2.0) Recombinant heme pocket amino acid modified polymerized Hb	Baxter Healthcare	10	Development terminated
O-raffinose cross-linked and polymerized Hb	Hemolink Hemosol Inc.	10	Phase II coronary artery bypass graft terminated
Polymerized human Hb pyridoxilated	Polyheme Northfield laboratories	14–15	Phase III trauma
HBOC-201 Glutaradlehyde polymerized bovine Hb	Hemopure Biopure Corporation	13	Surgical anemia in orthopedic surgery (Biologics application data review completed by FDA)
(PHP) Pyridoxilated Hb Polyoxyethylene	Curacyte Inc. (previously apex Bioscience)	8.0	Phase III shock associated with SIRS
(MP4) MalPeg 4 maleimide—PEG 5000 conjugated Hb	Hemospan Sangart Inc.	4.2	Preclinical (US) pilot human safety (Sweden)
(ZL-Hb) Zero-length (link) polymerized bovine or human Hb	IPBL pharmaceuticals (patented by University of Maryland)	6	Preclinical
(HbV/HAS) Polyethylene glycol decorated liposome encapsulated Hb suspended in human serum albumin	Developed by Keio and Waseda Universities, Tokyo, Japan	8.6	Preclinical

(Adapted from Buehler PW, Alayash AI. Toxicities of hemoglobin solutions: in search of in-vitro and in-vivo model systems. *Transfusion.* 2004;44(10):1516–1530.)

carry large amounts of dissolved oxygen. Unfortunately, subsequent clinical trials failed to show efficacy in the treatment of anemia due to hemorrhage.

The second generation PFCs appeared promising when utilized in conjunction with isovolemic hemodilution, but these trials in the setting of cardiac surgery were recently terminated. Despite many years of research and numerous attempts at developing a safe and effective product, the ideal blood substitute still eludes scientists and clinicians. Baxter Pharmaceuticals has stopped all research

TABLE 10.3
POTENTIAL PROBLEMS IN THE USE OF HEMOGLOBIN SOLUTIONS

- Pulmonary hypertension.
- Excessive vasoconstriction and toxic effects on the organs.
- Oxidative damage.
- Platelet activation.
- Immunomodulation.
- Increased susceptibility to infection.
- Interference with blood tests.

(Adapted from Creteur J, Sibbald W, Vincent JL. Hemoglobin solution—not just red blood cell substitutes. *Crit Care Med.* 2000;28(8):3025–3034.)

and development efforts on this product due to the poor results obtained thus far. The studies were terminated because of negative results in the experimental groups. It is unclear if these were due to design, selection, or drug response (Table 10.3).

Northfield Laboratories is currently involved in a phase III study (in collaboration with the U.S. Army) designed to evaluate the safety and efficacy of PolyHeme when used to treat patients in hemorrhagic shock following traumatic injuries.

Hemosol studied the efficacy of Hemolink (*o*-raffinose cross-linked hemoglobin) in a phase III trial in avoiding red blood cell (RBC) transfusion or in reducing the number of units transfused in coronary artery bypass graft patients. Overall, a lower number of RBC units were transfused in the Hemolink group (49 units) as compared to the control group (104 units). However, the trial was terminated due to an increased incidence of cardiac adverse events (particularly myocardial infarction) in the Hemolink group compared to placebo.

Biopure has conducted or sponsored more than 200 preclinical animal and laboratory studies of its oxygen therapeutics and about 22 phase I–III clinical trials of its product Hemopure (purified hemoglobin from refined cow's blood). Most of these studies have shown a clear benefit in terms of transfusion avoidance with acceptable rates and types of cardiac events (72–74). Currently, the U.S. Naval Medical Research Center (NMRC) is involved in a collaborative research and development agreement (CRADA) with Biopure to fund and conduct a randomized, standard therapy controlled trial of Hemopure in out-of-hospital resuscitation of patients with severe hemorrhagic shock. This study entitled "Restore Effective Survival in Shock" (RESUS), is intended to support an indication for out-of-hospital military and civilian trauma applications.

In December 2003, Biopure began a multicenter phase II clinical trial in Europe as a pilot safety study of Hemopure in the setting of elective angioplasty and stent procedures in percutaneous coronary intervention (PCI). Its goal is to assess the safety of the product as a potential cardioprotective agent in adult patients with coronary artery disease. Approximately 45 patients will be evenly randomized to receive either placebo or 15 or 30 grams of hemoglobin in the form of Hemopure intravenously before undergoing PCI. Patients will be monitored until discharge and at 30 days postinfusion.

CONCLUSION

At present, future ability to fully replace the oxygen-carrying capacity of packed red cells is in doubt. However, research has produced products that hopefully will alleviate or decrease the need for blood transfusions in the operating room and trauma settings, which resort most frequently to red cell transfusions. Research in the surgical setting and in acute blood loss resulting from trauma should shed light on the safety and future applicability of hemoglobin substitutes to other settings, such as anemia resulting from cancer. Further means of decreasing transfusions of packed red blood cells will become increasingly necessary as the population ages and the blood donor pool diminishes.

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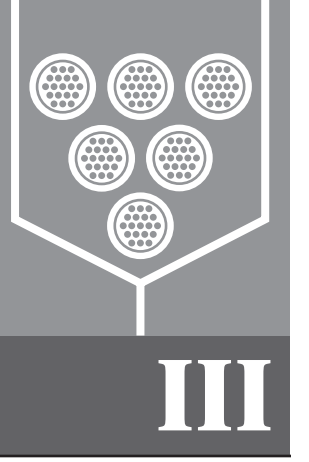
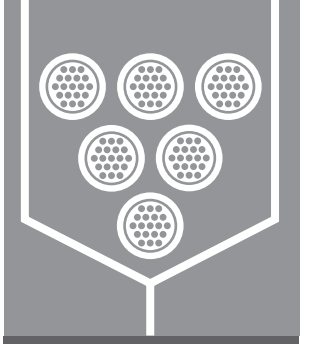


Transfusion Risks



Infectious Risks of Transfusion

11

Eberhard W. Fiebig *Michael P. Busch*

Infectious disease transmission has always been a concern for blood bank professionals and for practicing physicians who prescribe blood products for their patients. In the late 1930s, when modern day transfusion therapy began, syphilis was the most frequently recognized transfusion-transmitted infectious disease (TTID) (1). Presence of the causative spirochete bacteria in the blood stream of asymptomatic donors was not uncommon in the preantibiotic era, and transfusion of fresh, unrefrigerated whole blood facilitated transmission of this fastidious pathogen at that time. Posttransfusion hepatitis (PTH) was, until recently, the most common infectious risk of transfusion. It was already recognized and described in the early 1940s (2). However, it took 30 years of progress in science and technology until the first blood donor screening test for one of the major viruses causing PTH (hepatitis B virus, HBV) could be implemented, and another 20 years until a sensitive test for the main virus responsible for PTH (hepatitis C virus, HCV) was available for blood donation screening in the early 1990s. The sentinel event that directed unprecedented public attention to the problem of infectious disease transmission by transfusion occurred a decade earlier in the early 1980s. The discovery of the human immunodeficiency virus (HIV), etiologic agent of acquired immunodeficiency syndrome (AIDS), and establishment of HIV as a transfusion-transmitted organism quickly and dramatically raised awareness about the threat of infectious risks of transfusion, and made protection of the blood supply from infectious agents a public health priority (3). Since then, intensified blood donor evaluation, deferral of high risk donors, and successive implementation of more sensitive screening tests (Fig. 11.1) (Table 11.1) has minimized infectious risks of transfusion (Table 11.2), particularly with respect to transmission of HIV and HCV which now carry a risk of less than 1 per million units transfused (4,5).

Despite this impressive achievement, concerns over residual risks from established TTIDs, foremost AIDS, hepatitis, and bacterial sepsis continue, and emerging infections precipitate new alarms over the safety of the blood supply on an annual basis. The latter category includes recently discovered entities such as variant Creutzfeldt-Jakob disease (vCJD) and Severe Acute Respiratory Infection (SARS), for which transmission by transfusion is considered possible but has not been proven, and longer known exotic infectious diseases, such as West Nile Virus (WNV) meningoencephalitis, Chagas disease, and babesiosis that are newly or increasingly encountered as TTIDs.

This chapter reviews the agents that are established or implicated causes of TTIDs, discusses infectious risks for transfusion recipients, and provides a perspective of current and anticipated measures to protect the blood supply from the threat of pathogen transmission. A section on autologous transfusion addresses specific issues surrounding this procedure from an infectious disease point of view. Readers looking for more in-depth information on these topics are referred to standard infectious disease (6) and transfusion medicine texts (7,8).

RETROVIRUSES

Retroviruses owe their name to reverse transcriptase, an essential enzyme in the viral life cycle that allows transcription of viral RNA to DNA after infection of a host cell. They

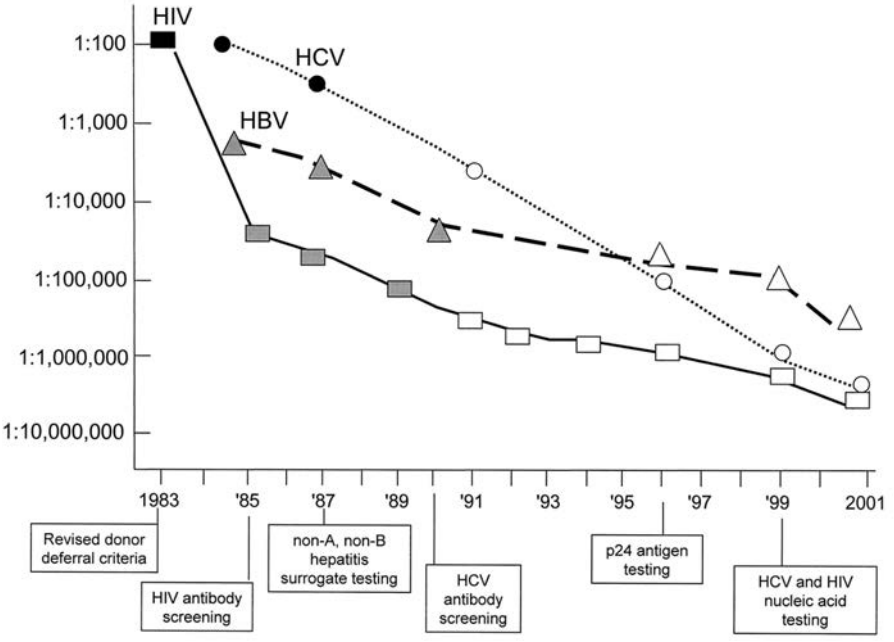


Figure 11.1 Decline in human immunodeficiency virus (HIV), Hepatitis B (HBV), and Hepatitis C (HCV) risks of transmission through transfusion. Data were derived from studies sponsored by the National Heart, Lung, and Blood Institute. Specific references are available from the authors upon request. Estimates before 1991 are based on donor prevalence measurements (black data markers) or recipient follow-up studies (gray data markers; estimates after 1991 represent projections based on mathematical modeling (open data markers). Estimated risk of infection per unit transfused in 2000–2001, the most recent period for which data is available was approximately 1: 200,000 for HBV and nearly 1:2,000,000 each for HCV and HIV (see Table11.1). (Reprinted with permission from Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *JAMA*. 2003;289: 8:959–962.)

form a diverse family of viruses, currently divided into seven genera, which infect numerous vertebrate species, including man. Two human retroviruses, HIV, a member of the lentivirus genus, and the human T-cell leukemia virus (HTLV), which forms its own genus together with simian and bovine leukemia viruses, stand out as transfusion-transmissible pathogens.

TABLE 11.1
ROUTINELY PERFORMED INFECTIOUS DISEASE SCREENING TESTS ON U.S. BLOOD DONATIONS IN 2005

Pathogen	Screening Test
Treponema pallidum	Standard Serological Test (STS) for syphilis
Hepatitis B Virus (HBV)	HBV surface antigen (HBsAg) Antibody to HBV core antigen (anti-HBc)
Hepatitis C Virus (HCV)	Antibody to HCV (anti-HCV) Nucleic Acid Test (NAT) for HCV RNA
Human Immunodeficiency Virus (HIV)	Antibody to HIV1/2 (anti-HIV-1/2) NAT for HIV-1 RNA
Human T Cell Lymphotropic Virus (HTLV)	Antibody to HTLV I/II (anti-HTLV-I/II)
West Nile Virus (WNV)	NAT for WNV RNA

Human Immunodeficiency Virus-1 (HIV-1)

Initial reports of acquired immunodeficiency syndrome (AIDS) in hemophiliacs (9) and transfusion recipients (10) were published in the early 1980s. Subsequent studies unequivocally established transmissibility of the causative agent (HIV) by untreated coagulation factor concentrates and blood components (11). Over 9,000 AIDS cases in the U.S. were linked to transfusion through December 31, 2001 (12), and an additional 5,000 patients with hemophilia and other coagulation disorders acquired AIDS as a result of therapy with plasma derivatives (3). Most transmissions in the U.S., and other developed countries, occurred early in the epidemic, before deferral of high risk blood donors (mostly gay men, their sex partners, and intravenous drug users). Implementation of donor screening with HIV antibody tests in 1985 drastically reduced the risk of transfusion-transmitted HIV infection. Since then, less than 50 cases of transfusion-related HIV transmissions have been reported from screened blood. Almost all of these cases were so-called "window period" transmissions where the blood donor was newly infected, asymptomatic, and had not yet produced antibodies that allowed detection by the antibody test. Since high-level viremia precedes the appearance of detectable antibody by days to weeks in typical primary HIV infections, blood donations from these individuals are usually highly infectious.

Sequential introduction of improved, highly sensitive enzyme immunoassays for detection of antibodies to HIV type-1 (HIV-1) in the early 1990s, addition of testing for HIV-1p24 antigen in 1995, and HIV-1 RNA testing on pooled

TABLE 11.2
CURRENT RISK ESTIMATES OF TRANSFUSION-TRANSMITTED DISEASES IN THE U.S.

Pathogen	Average Estimated Risk Per Unit
Hepatitis A	Unknown, presumably <1:1 million
Hepatitis B	1:205,000[a]
Hepatitis C	1:1,935,000[b]
Human Immunodeficiency Virus-1	1:2,135,000[b]
Human T-Lymphotropic Virus-I, II	1:2,993,000
Cytomegalovirus (CMV)	Infrequent with leukocyte-reduced components
Parvovirus B19	Unknown, presumably <1:1 million
West Nile & other Arbo Viruses	Regional and seasonal risk, observed incidence of transmissions during 2003 season after implementation of pooled NAT approximately 1:1 million recipients
Bacterial contamination associated with symptomatic sepsis	1:5 million per red blood cell unit[d] 1:100,000 per apheresis or pooled platelet unit[c]
Malaria	<1:1 million
Babesia	<1:1 million, higher in endemic areas
Chagas disease	unknown, presumably <1:1 million
Creutzfeldt-Jakob disease (CJD), vCJD	single probable case reported in UK

[a]Estimates for HBV reflect risk projections prior to implementation of blood donor screening with nucleic acid testing (NAT). (Adapted from Dodd RY, Notari EPT, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion*. 2002;42(8):975–979.)
[b]Estimates for HIV, HCV indicate risk projections following implementation of NAT for these agents in 1999. (Adapted from Dodd RY, Notari EPT, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window-period risk in the American Red Cross blood donor population. *Transfusion*. 2002;42(8):975–979.)
[c]Risk estimate reflects the experience of a 2-year U.S. national study from 1998 to 2000, prior to implementation of standards to detect and limit bacterial contamination. Due to likely under-reporting, true risks were probably higher. (Adapted from Kuehnert MJ, Roth VR, Haley NR, et al. Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. *Transfusion*. 2001;41(12):1493–1499. Modified with permission from Fiebig EW, Busch MP. Emerging infections in transfusion medicine. *Clinics in Laboratory Medicine*. Philadelphia: WB Saunders, Elsevier, 2004;23(4):797–823.)

donor samples in 1999, reduced the risk of HIV transmission by transfusion to its current low level of about 1 per 2 million units transfused (4,5,13). The risk for manufactured blood products, such as coagulation factor concentrates, albumin and immune globulin preparations, can be expected to be even lower because of additional viral inactivation processes, including heat (pasteurization), physico-chemical processes (solvent/detergent treatment), and nanofiltration that have been implemented since the mid 1980s. Since then, no new HIV infections have been attributed to manufactured plasma-derived products (14,15).

Blood centers notify donors found repeatedly reactive in HIV antibody screening tests with appropriate counseling messages, even if confirmatory or supplemental testing results by Western blot (WB) or immunofluorescence are negative or indeterminate. Donors with positive and persistently indeterminate WB are permanently deferred from giving blood for use in transfusion. Studies indicate that few blood donors with indeterminate results by HIV supplemental tests are infected with HIV (16), and that low risk blood donors on occasion may have false positive supplementary test results (17). Recipients of prior donations from donors with confirmed positive results are traced through mandatory look-back investigations with the goal of offering them counseling and testing for HIV infection. Because of long-standing implementation of sensitive screening assays and low incidence rates of HIV infection among blood donors, few look-back investigations are triggered by confirmed reactive screening assays nowadays. This is in contrast to the first decade of the HIV epidemic, when it was not uncommon to perform look-back on prior donations from blood donors who tested either seropositive following donation or were implicated because of presumed transfusion-associated HIV infection in the recipient.

Human Immunodeficiency Virus-2

Human immunodeficiency virus, type-2 (HIV-2), a retrovirus linked more closely to the simian immunodeficiency virus than to HIV-1, was recognized initially in West Africa in the late 1980s. Sixty-two cases of HIV-2 were reported in the United States by mid 1995, the most recent date when prevalence rates of the infection were reported. Transmissibility of HIV-2 appears to be lower, and the course of infection milder with the interval between infection and clinical AIDS longer than for infections associated with HIV-1 (18).

Antibody testing using assays developed for HIV-1 detects 60% to 91% of HIV-2 infected persons, whereas HIV-2 antibody test kits detect >99% (19). Blood donor testing using sensitive combination assays for both HIV-1 and HIV-2 antibodies began in 1992. As of 1998, only three donors with HIV-2 infection were identified in the U.S. after screening more than 50 million donations, suggesting a very low risk for breakthrough HIV-2 transmission by transfusion (20).

HIV-1 Group O and Group M Subtype Infections

The HIV-1 group O (outlier group) viruses were isolated from patients in Central and West Africa in 1994. These

HIV-1 variants share 65% to 70% genomic sequence homology with HIV-1 and 56% with HIV-2. Through 1997, two HIV-1 group O-infected persons were identified in the United States (21). To safeguard against possible false-negative HIV antibody test results in blood donor screening (22), blood donors are deferred if they were born in, lived in, traveled to West Africa and received a blood transfusion, or had other parenteral exposures in HIV-1 group O endemic African countries (23). The FDA has also stipulated that HIV-1 antibody assays intended for donor screening must in the future demonstrate HIV-1 group O sensitivity prior to licensure.

The majority of HIV-1 infections are caused by subtypes of group M (main group) viruses. In the U.S. and Europe almost all HIV-1 infections are caused by subtype B viruses, but worldwide other subtypes dominate locally (24). At least in the past, widely used antibody assays for detection of HIV-1 infection were based on, and optimized for, rapid detection of subtype B infections, and did not perform as well with non-subtype B viral strains (25), raising concern that infections with such strains could be missed. The introduction of nucleic acid technology (NAT) assays into blood donor screening has resolved this issue, since these tests have been designed to perform well in detection of all group M subtypes. Ongoing surveillance studies monitor emergence of new HIV variants and the effectiveness of routine HIV test kits for detecting these viruses.

Human T-Lymphotropic Virus-I and Human T-Lymphotrophic Virus-II

HTLV-I and HTLV-II are closely related retroviruses which share 60% to 70% genomic sequence homology and tropism for T lymphocytes. In contrast to HIV, HTLV is rarely present in cell-free plasma and shows little active replication in infected humans. HTLV is found around the globe with endemic foci in southern Japan, the Caribbean, certain parts of South America, Africa, the Middle East, and Melanesia (26). An epidemic of HTLV-II infection has been observed over the past 40 to 50 years among intravenous drug users in the U.S., Brazil, and Europe (27,28). Transmission of both HTLV-I and HTLV-II occurs by parenteral exposures, through sexual contact, and by vertical transmission from mother to child during pregnancy and breast feeding.

Diseases associated with HTLV-I infection include adult T-cell leukemia/lymphoma (ATL), HTLV-associated myelopathy/tropical spastic paraparesis (HAM/TSP), lymphocytic pneumonitis, uveitis, polymyositis, and arthritis (29). HTLV-II does not appear to cause hematological malignancy but has been associated with the other conditions attributed to HTLV-I infection, and also has been linked to a higher rate of common infections such as acute bronchitis, pneumonia, and urinary tract infections, suggesting a mild immunosuppressive effect of the virus (30).

Patients with ATL have HTLV-I provirus integrated into malignant CD4+ flowerlike cells (31). ATL occurs in 2% to 4% of infected persons following a latent period that extends to several decades. The illness is characterized by leukemia, generalized peripheral lymphadenopathy, hepatomegaly, impaired liver function tests, splenomegaly, skin lesions, bone lesions, and hypercalcemia (32,33). HAM/TSP occurs in approximately 2% of HTLV-I infected individuals. Patients with transfusion-associated HAM/TSP develop neurologic symptoms at a median of 3.3 years after transfusion (32,33). This illness is characterized by slowly progressive chronic spastic paraparesis, lower limb weakness, urinary incontinence, impotence, sensory disturbances, low back pain, hyper-reflexia, and impaired vibration sense.

Risk factors for both HTLV-I and HTLV-II infections in U.S. blood donors include low educational attainment, accidental needle sticks, previous blood transfusion, frequent sex partners, and a sex partner from an HTLV endemic area. In contrast, injection drug use or having sex with a drug user associates significantly with HTLV-II but not with HTLV-I infection (34).

Blood donor screening for HTLV-I antibodies began in the U.S. in 1988, and a more sensitive HTLV-I/II combination assay that detects close to 100% of HTLV-II infections was introduced in 1998 (35). Both the prevalence rate of confirmed HTLV infection among first time blood donors and incidence rates in repeat donors decreased about 10-fold during the 1990s (4). Based on the most recent available incidence rates, the window period risk of HTLV exposure through blood transfusion was estimated to be about 1 in 3 million units transfused in 2001 (4). Since essentially cell-free components such as plasma and cryoprecipitate generally do not transmit HTLV and only 30% of infected cellular components result in transmission (36), the threat of acquiring HTLV infection from screened blood appears to be minimal at this time. The trend toward universal leukocyte reduction of cellular blood components, i.e., red blood cells and platelets, can be expected to further lower the risk of HTLV infection for transfusion recipients.

HEPATITIS VIRUSES

Viruses that target and induce damage of human hepatic cells may be classified into those that are primarily transmitted by the fecal–oral route (hepatitis viruses A and E) and others that are preferentially spread through parenteral

contact, i.e., through infectious blood or body fluids (hepatitis viruses B–D, G, and others). The former viruses cause outbreaks of acute hepatitis in community settings, but are rarely transmitted by transfusion. Hepatitis viruses B and C in the latter group are the agents that are classically associated with posttransfusion hepatitis.

Predominantly Enterally Transmitted Hepatitis Viruses (Hepatitis A and E)

The hepatitis A virus (HAV), a non-enveloped RNA virus in the picornavirus family, is transmitted predominantly through the fecal–oral route, causing frequent epidemics of acute hepatitis in low income countries, with occasional focal outbreaks in the U.S. and other resource rich nations (37). The incubation period averages 28 days (range 15 to 50 days) and signs or symptoms persist for less than 2 months. Approximately 10% to 15% of infected individuals develop prolonged or transient relapsing illness, but HAV is always self-limited with no chronic or carrier state. HAV is the most frequent cause of hepatitis among children under 11 years of age. Risk factors for acquiring infection include close personal contact with infected individuals and injection drug use. Approximately 45% to 50% of those infected have no identifiable transmission source. Preceding onset of jaundice or elevation of liver function tests is a period of asymptomatic viremia which may be present up to 30 days before onset of symptoms, longer than previously recognized (38). Nevertheless, transmission by transfusion occurs infrequently, presumably considerably less than 1 per million units transfused. When transfusion transmission has been recognized it was typically traced to blood donation by a recently infected, asymptomatic individual (39).

Of greater concern has been the relative resistance of the hepatitis A virus to inactivation steps used in the manufacture of plasma derivatives. Several outbreaks of acute hepatitis A from contaminated clotting factor preparations have been reported (40,41). Fortunately, owing to differential distribution of contaminating HAV away from plasma fractions that give rise to albumin or plasma protein fractions, and usual presence of anti-HAV in immune globulin preparations, these products have not been implicated in HAV transmission (42). It can be expected that with newer and additional viral inactivation methods that are now being used, combined with nucleic acid testing of source plasma pools for HAV, clotting factor concentrates will also be safe in regard to HAV transmission. Because of the remote risk of HAV transmission from transfusion, routine screening of blood donors with NAT technology has not been recommended.

The hepatitis E virus (HEV), a non-enveloped RNA calicivirus often associated with fecal-contaminated water supplies, usually causes a self-limited illness. Epidemic outbreaks of HEV infection are common in low income, tropical countries around the globe where the virus is endemic; sporadic transmissions have been described in North America, Europe, and Japan. Transmission by transfusion has long been considered a possibility, particularly in countries where HEV is endemic, but definitive evidence has been lacking (43). A recent report from Japan describes a case of HEV transmission confirmed by genomic sequence identity of viral isolates in the donor and recipient (44). The transmitting component was a unit of fresh frozen plasma. The recipient was diagnosed with acute hepatitis 24 days after transfusion and recovered within 3 months; the donor remained asymptomatic.

Parenterally Transmitted Hepatitis Viruses

Hepatitis B Virus

The hepatitis B virus (HBV) is a member of the Hepadnavirus (hepatotropic DNA virus) family. The infectious virion (Dane particle) consists of an outer envelope that is rich in antigenic lipoprotein, known as hepatitis B surface antigen (HBsAg), and an inner nucleocapsid, composed of a shell of hepatitis B core (HBc) protein, viral DNA, polymerase with associated X-proteins needed for viral replication and hepatitis B early antigen (HBe), named after its early appearance during HBV infection. A characteristic feature of viral replication is the formation of noninfectious particles composed predominantly of HBsAg lipoproteins (hepatitis B spheres and filaments), which exceed infectious Dane particles in blood by 1,000-fold to 10,000-fold (45).

The usual incubation period of HBV infection is 4 to 10 weeks but may last as long as 6 months. The clinical presentation and course is largely dependent on the age when infection occurs. Adults, although often asymptomatic, are more likely than children to experience jaundice and other signs and symptoms of acute hepatitis, but rarely (generally less than 5%) develop chronic disease, while 90% of neonates and 30% of children age 1 to 5 become chronically infected. In a 1976 to 1994 survey, approximately 5% of the United States population had serologic evidence of HBV infection and 1.25 million were thought to be infected chronically (46). Due, in a large part, to vaccination of infants which began in the early 1980s the incidence rate (number of new infections in the population per year) has declined 67%, from 8.5 per 100,000 in 1990 to 2.8 per 100,000 in 2001 (47). Among blood donors, the number of new HBV infections declined from 1.97 to 1.27 per 100,000 person-years between 1998 and 2001 (4).

Transmission of HBV occurs parenterally through contact with infectious virus in blood and body fluids. Viral

titers in blood are significantly greater than those present in semen, vaginal fluid, and saliva. In relative terms, HBV appears to be one hundred times more infective than HIV and ten times more infective than HCV (48). The most frequent mode of transmission in adults and adolescents occurs through sexual contact. Forty percent of those infected with HBV have partners that are also infected, 15% are males having sex with other males, injecting drug users account for 14% of cases, and one third have no identifiable risk.

Markers of HBV infection appear in plasma in characteristic sequence following a transmitting exposure. HBV DNA detectable by nucleic acid amplification tests appears first, within several weeks of inoculation using the most sensitive assays and preceding HBsAg detection by 2 to 4 weeks (49). HBsAg and HBeAg are typically detectable 4 to 8 weeks (30 to 60 days) after infection, followed within a few weeks by IgM-class anti-HBc antibodies whose appearance coincides with onset of symptoms and high levels of transaminase enzymes in blood. High viral titers (10^{10} genomic copies per mL) are present at this time, but decline subsequently; the concentration of HBsAg correlates with higher titers of HBV and greater infectivity during this acute stage of infection. HBeAg and HBsAg persist in acute resolving infections for up to 4 months (average 63 days). Antibodies against HBsAg (anti-HBs) emerge subsequently and protect against reinfection. Detection of anti-HBc in the absence of HBsAg and anti-HBs may be indicative of chronically infected, low level carriers; some of these individuals contain circulating HBV DNA and have been demonstrated to be infectious by transfusion (50). Although anti-HBs confers immunity, sufficient virus remains in the liver to transmit HBV following liver transplant from anti-HBs positive donors (51).

Prevention of HBV transmission by transfusion relies on exclusion of high risk blood donors and screening of blood donations for HBsAg and antibodies to HBcAg (anti-HBc). The value of anti-HBc testing has been questioned, but this test may provide protection from transmission by low level chronic carriers and in case of rare infectious HBV mutants that lack HBsAg (52). With these serological screening tests in place, rare residual cases of transfusion transmitted HBV infections are generally due to blood donations from acutely infected asymptomatic donors who present prior to HBsAg appearance, i.e., during the approximate 59-day (range 37 to 87 days) "window period" (53,54). The current risk estimate of blood donations screened with HBsAg and anti-HBc is approximately 1 per 205,000 units (4,5). Further risk reduction can be expected from recently implemented high sensitivity serologic assays for HBsAg that detect approximately 0.1 ng per mL HBsAg compared to an average of 0.3 ng per mL with previous assays, and HBV NAT on either single donation samples or samples from multiple donors in minipools (49). NAT on single donation samples has the potential to reduce the risk of transfusion-transmitted HBV by detecting newly infected donors 21 to 29 days earlier than currently licensed HBsAg tests; minipool testing on the other hand offers little improvement over current and new investigational HBsAg assays for donor screening (49).

Hepatitis C Virus

The hepatitis C virus (HCV) is an RNA virus in the Flaviviridae family. Six genotypes and multiple subtypes have been described on the basis of relatedness in genome sequence. In the United States and western Europe, genotypes 1a and 1b are most common, followed by genotypes 2 and 3. Other genotypes are rare in these geographic areas but are common in Africa and Asia. The significance of genotyping lies in prediction of response to antiviral therapy: genotype 1 responds less favorably than genotypes 2 or 3 (48).

The current disease burden from HCV infection in the U.S. is substantial, with approximately 1.8% of the population positive for HCV antibodies, 2.7 million chronically infected, and 25,000 newly infected persons annually (55). Prevalence and incidence rates among U.S. blood donors are approximately one fifth of that in the general population (56). Risk factors most strongly associated with HCV infection are injection drug use and receipt of a blood transfusion before implementation of blood donor screening for HCV in 1990. Other risk factors include iatrogenic and nosocomial exposures in health care and similar institutions, poverty, intranasal drug use, and sexual and vertical transmission. In contrast to HIV and HBV infections, the latter two modes of transmission are considered relatively inefficient for spreading of HCV.

Characteristic clinical features of HCV infection that make this disease a public health hazard are a lack of symptomatic acute infection (only 20% to 30% of newly infected persons report symptoms) and a tendency toward chronicity with a high titer asymptomatic carrier state. Chronic hepatitis develops in 75% to 85% of persons infected after 45 years of age and 50% to 60% of those infected as children or young adults (57,58). Of patients with chronic HCV infection, approximately 25% develop fibrosis that evolves into cirrhosis over an average 20-year interval. Biochemical evidence of liver inflammation occurs in 70% of those infected as adults compared to 10% of those infected as juveniles. The risk of progression to cirrhosis varies from 10% to 20% of those infected as adults to approximately 5% of those infected earlier in life (57,58). Alcohol consumption increases the risk of progression to

cirrhosis. Hepatocellular carcinoma occurs in 1% to 4% per year in those with cirrhosis.

The risk of HCV transmission by transfusion declined dramatically following sequential introduction of serologic and later NAT testing for HCV during the 1990s. The current risk estimate for HCV transmission from a blood component is 1 per 1,935,000 units (4). The remarkable advances in safety achieved by HCV NAT greatly reduced transfusion associated HCV cases. Nonetheless, some newly infected individuals demonstrate fluctuations in HCV RNA, at times below NAT detection levels prior to HCV antibody seroconversion. This possibly explains some of the low residual risk of transfusion-transmitted HCV infection despite the ongoing combination of HCV antibody and NAT testing (59).

In an effort to identify transfusion recipients who may have been infected before reliable HCV blood donor screening became available in 1992, or who received blood from a donor who was later found to be infected with HCV, look-back procedures were put in place, analogous to those that already had been in effect for HIV. Unfortunately, only a minority of the recipients are reached through these programs, and their overall benefit in identifying previously unrecognized persons with HCV for counseling and testing purposes, has been limited (60,61).

Hepatitis D Virus

Originally called the delta agent, this is a defective RNA-containing passenger virus that requires HBV to act as a "helper" for assembly of envelope proteins (62). Screening for hepatitis B acts synergistically in preventing transfusion associated hepatitis D cases by identifying donors that are coinfected with hepatitis B and D.

Non-A–E Hepatitis Viruses

Following discovery of HCV, few cases of apparent viral hepatitis remained in which none of the classical hepatitis viruses A–E, nor any of the other viruses known to cause hepatitis, could be identified as a causative agent. In the search for the elusive pathogen(s) several candidate viruses were identified, but to date these do not appear to specifically target liver cells or be causally linked to hepatic injury.

The first presumptive novel agent, hepatitis G virus (GBV-C), is related to the Flavivirus group and thus shares similarities with HCV. The predominant mode of transmission of GBV-C is through parenteral exposure. Infection occurs frequently among those infected with HCV and HIV but is also evident in the general population at rates in the 1% to 3% range in countries around the globe. Approximately 2% of blood donors and 15% to 20% of injection drug users in the U.S. have detectable GBV-C RNA, and additional persons have antibodies against E2 envelope protein in the absence of GBV-C RNA suggesting viral clearance. Importantly, epidemiological studies have shown no association of GBV-C infection with liver disease and it is not clear if the virus plays a role in pathogenesis elsewhere (63,64). Interestingly, observations in persons coinfected with GBV-C and HIV point to a protective effect of GBV-C on HIV disease progression (65). The mechanism of this intriguing finding is presently unclear.

Two related non-enveloped viruses, named TT and SEN after the initials of the patients from whom the first isolates were obtained, were identified in patients with hepatitis but in subsequent studies seem to lack association with clinical hepatitis (66). Both viruses were tentatively grouped with the circovirus family and share epidemiological characteristics, i.e., widespread distribution, efficient transmission by the parenteral routes including transfusions, and passage by additional modes of transmission. The reported prevalence of TT virus infection among blood donors varies widely from 2% to 90%, depending on the nucleic acid assays employed for screening. Transfusion-transmission of the virus probably occurs frequently but no disease consequences have been documented.

HUMAN HERPES VIRUSES

Human herpes viruses (HHV) are enveloped, structurally complex double stranded DNA viruses that cause a variety of common infectious diseases. HHV infection generally results in lifelong persistence of viral genetic material in the infected host with the possibility of recurrent reactivation infections. HHV are classified in 3 subfamilies, alpha-herpesvirinae, beta-herpesvirinae, and gamma-herpesvirinae. Viruses of concern for transfusion recipients are grouped among the latter 2 subfamilies; members of the alpha herpes virus subfamily, herpes simplex viruses and varicella zoster virus, rarely, if ever cause transfusion-transmitted infections.

Cytomegalovirus (HHV-5)

Cytomegalovirus (CMV), a beta herpes virus, can infect a wide range of cell types, including monocytes and myeloid progenitor cells of which the former represent the preeminent source of transfusion-transmitted infection (67). Primary CMV infection in immunocompetent individuals is usually community acquired and often asymptomatic or associated with a mild, self-limited infectious mononucleosis syndrome. However, in virtually all cases latent virus persists permanently in cellular reservoirs, allowing lifelong reactivation infections, or in the setting of transfusion or transplantation, viral transmission via cellular blood products or transplanted

donor organs. In fetuses, premature neonates and immunosuppressed patients, CMV infection may affect a wide range of organ systems and is often associated with considerable morbidity and mortality (68). Primary infection in pregnancy does not pose a threat for the woman but may cause severe fetal malformation syndromes and congenital infections associated with mortality rates approaching 20% (69).

Transmission of CMV by transfusion appears to occur primarily via latently infected CD14+ peripheral blood monocytes (67). These cells can be found in low numbers in cellular blood components donated by healthy, asymptomatic individuals who were infected with CMV at some time in the past, as evidenced by the presence of antibodies to CMV. More than 40% of blood donors in the U.S., and worldwide, fall into this latent infection category, creating a significant potential for transfusion-transmitted CMV infection. Fortunately, this is primarily a concern only for recipients who are at risk for significant disease by virtue of pregnancy, immaturity, or immunosuppression. Among seronegative, immunocompetent recipients, seroconversion as evidence of TT-CMV infection is rare (<1% in more recent studies), occurs preferentially in subsets of heavily transfused patients and is usually not associated with symptomatic disease (68). However, it should be pointed out that unless evidence of infection is looked for prospectively, it will probably not be found. On the other hand, seronegative recipients with an immature or suppressed immune system, such as neonates undergoing exchange transfusion or bone marrow transplant recipients, were frequently (>10% to 30%) infected in the past in the absence of CMV-safe blood products, and anywhere from <5% up to 50% of those infected suffered significant morbidity and mortality when no special precautions were taken to detect and treat TT-CMV. Blood products considered CMV-safe are plasma components (FFP, Cryoprecipitate), components prepared from seronegative blood donors, and leukocyte-reduced components containing $<5 \times 10^6$ white blood cells. No CMV transmissions have been reported from plasma transfusions, but 1% to 2% breakthrough infections have been observed with use of either seronegative or leukocyte-reduced cellular blood components, with perhaps a slightly greater risk of infection and symptomatic disease with the latter approach. The controversy over whether both methods provide equal protection, has led many practitioners to opt to provide seronegative recipients at risk for symptomatic CMV infection with cellular components from seronegative blood donors, even if the component is also leukocyte-reduced, and to rely on leukocyte reduction alone only if seronegative components are unavailable. To ensure best practices, given local circumstances, it has been recommended that each institution review its internal policies for blood use in patients vulnerable to serious CMV infection (70). If leukocyte reduction is chosen as a means to reduce the risk of CMV transmission, components prepared by prestorage-leukocyte reduction at blood collection facilities should be selected because leukocyte removal by this method is more reliable than bedside filtration (70,71).

Transplant patients warrant special consideration. Although CMV seronegative renal and liver transplant recipients are at risk for symptomatic transfusion-transmitted CMV infections, the risk associated with receiving seropositive solid organs far outweighs that attributed to blood transfusion. Consequently recipients of seropositive organs are not considered candidates for CMV-safe blood components. CMV-seronegative HIV-infected patients represent another group at risk for transfusion-transmitted primary CMV infection (Table 11.2), although the vast majority of HIV infected patients have preexisting CMV infections and are at greater risk of reactivation disease than transfusion-related CMV complications (68).

CMV seropositive patients theoretically remain at risk for second strain infections. These have been reported in immunocompetent patients, where they appear not to be associated with added morbidity, and in recipients of solid organ transplants, where they do contribute to more severe disease than from reactivation of endogenous virus (68,71). The source of second strain infections in the latter setting is frequently the transplanted organ, while evidence linking blood transfusions as the source is not available. Furthermore, because reactivation of latent infections is a common occurrence in seropositive immunosuppressed patients, the benefit of providing reduced risk CMV components for these patients is unproven and this practice is generally not recommended.

Ex vivo and observational clinical studies suggest a link between allogeneic leukocytes in blood transfusion and reactivation of latent viral infection (72), providing an argument for using leukocyte-reduced blood to decrease infections in immunosuppressed CMV seropositive patients. While theoretically compelling, the effectiveness of this approach has not been demonstrated in prospective studies for CMV (73), or for that matter for other viruses (74,75).

Further risk reduction of transfusion transmitted CMV infection will likely depend on more complete understanding of viral reactivation in transfused passenger monocytes. Blood donor screening with NAT assays, which has been helpful in reducing the transmission risk of HIV and HCV by detecting plasma viremia during primary infection preceding antibody production, is unlikely to be

effective in preventing transmission of CMV. Even though primary infection with CMV occurs at a rate of approximately 1% per year in asymptomatic blood donors, plasma viremia is low grade and short-lived during this period. Plasma viremia also rarely occurs in asymptomatic seropositive donors, and is generally absent in seronegative donors who are not in the "window period" prior to seroconversion (76,77).

Epstein-Barr Virus (HHV-4)

Epstein-Barr virus (EBV), a gamma herpes virus, is the etiologic agent of heterophile antibody-positive infectious mononucleosis and is closely associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and posttransplant lymphoproliferative disease (PTLD) (78). Transfusion transmission of the virus is unlikely because more than 90% of the adult population has evidence of previous exposure and immunity to reinfection. Rare cases of transfusion-transmitted EBV presenting as infectious mononucleosis have been described in both immunocompetent recipients (79,80) and in immunosuppressed patients following solid organ transplantation (81). Aggressive EBV-associated lymphoproliferative disorders have been observed in patients with weakened immune systems following cord blood stem cell transplantation (82), but have not been documented following blood transfusion. Since B lymphocytes are the likely source of transfusion transmitted EBV infection, leukocyte reduction of cellular blood components which efficiently removes B cells is an attractive strategy to prevent infection in transfusion recipients (83). However, the validity of this assumption has yet to be established in controlled clinical trials.

Human Herpes Virus 8 (HHV-8)

HHV-8—a gamma herpes virus linked to Kaposi's sarcoma, body-cavity-based lymphoma, and Castleman's disease—has tropism to lymphocytes and monocyte-macrophages and has been shown to be transmitted by transplantation, but definitive evidence of transmission by transfusion is lacking (84,85). Past infection with HHV-8 among U.S. blood donors appears to be low (3% to 3.5%) and no evidence of viremia was observed in one large multicenter study (84). These findings are in agreement with epidemiological studies that suggest sexual contact is the preferred route of HHV-8 transmission while blood-borne transmission appears to be an unlikely event (86). A greater potential of HHV-8 transmission by transfusion may exist in sub-Saharan Africa where HHV-8 DNA was reported in approximately 20% of investigated blood donors (87,88).

PARVOVIRUS B19

Parvovirus B19 is a small, non-enveloped DNA virus in the erythrovirus genus of the parvovirus family, so named after preferential propagation of the virus in eyrthroid progenitor cells (89,90). The virus has a global distribution with similar infection rates among populations worldwide. Natural passage is through respiratory droplets and secondary infections are common among those with close contacts, resulting in small epidemics in susceptible populations. Infection is common in children, where it is often associated with a characteristic facial rash that is responsible for its common name (slapped cheek or fifth disease after the day when the rash appears). Nonimmune adults may also be infected, but instead of a rash the infection is more likely to be accompanied by an immune-mediated inflammatory arthritis. Antiviral antibodies as evidence of past infection are found in 50% of 15-year-olds and an even higher rate in adults; presence of antibodies usually confers long-lasting immunity.

Pathogenesis involves attachment of the virus to the glycolipid globoside, also known as P antigen, on erythroid precursor cells. Individuals who lack the P antigen are not susceptible to infection. The primary disease manifestation, besides fever and nonspecific flulike symptoms, is a transient disruption of red cell production. Due to the long life span of normal red cells, temporary cessation of erythropoiesis goes unnoticed in otherwise healthy individuals, but may result in severe aplastic crises in patients depending on a high red cell reproduction rate, i.e., those with hemolytic disorders such as sickle cell anemia or thalassemia. Others at risk for aplasia following parvovirus infection include immunodeficient patients, HIV-infected patients, solid organ transplant recipients, and children with malignancies. Immunocompromised patients may develop severe chronic anemia due to persistent parvovirus infection. Acute parvovirus infection during pregnancy may result in fetal loss, neurological abnormalities, and congenital infection (91). RBC aplasia and chronic anemia due to parvovirus infection often respond to infusion with immune globulin preparations (90).

Parvovirus can be expected to be present in 0.025% to 0.1% of blood (92,93) and plasma donors (94) with even higher incidence rates that might occur during epidemic periods (90). However, protective antibodies are frequently present in the donor, recipient, or both, and only three transmissions of parvovirus due to single-donor

components have been reported (90). Of greater concern has been transmission via plasma-derived products, especially coagulation factor concentrates. This is due to the near ubiquitous presence of the virus in the large plasma pools that are the source material for these plasma products, and resistance of the virus to inactivation methods. As the experience with solvent detergent plasma has shown, the presence of neutralizing antibodies in the plasma pool does not guarantee protection from recipient infection (95). Prospective studies in previously untreated hemophilic patients who received virus-attenuated factor concentrates demonstrated a persistent 40% risk of parvovirus infection (96). Fortunately, these patients in general do not suffer serious or long-term hematologic sequelae regardless of HIV serostatus. Parvovirus B19 DNA has also been detected in albumin preparations, but infectivity of this product appears to be low or absent and no confirmed transmission has been reported (97). A recent report describes a single case where the B19 virus was transmitted via an immune globulin preparation, resulting in a life-threatening infection, marked by worsening of preexisting hepatitis and transient red cell aplasia (98).

NAT screening of source plasma for Parvo B19 DNA was implemented several years ago with the goal of excluding high level viremic donations from being used in the manufacture of plasma derivatives (94). This screening combined with improvement of nanofiltration procedures for plasma derivatives (99) promise to reduce the risk of parvovirus infection from these products.

WEST NILE AND OTHER MOSQUITO-BORNE VIRUSES

West Nile Virus (WNV) is a single-stranded RNA virus of the Flavivirus family and a member of the Japanese encephalitis virus serocomplex that includes Japanese encephalitis virus and St. Louis encephalitis virus (100). Viruses in this complex are arthropod-borne or arboviruses (i.e., transmitted by mosquitoes and arthropod vectors) with the potential to cause meningoencephalitis. WNV was first isolated in 1937 in the West Nile District of Northern Uganda and derives its name from that region. Over the next several decades its geographic range was found to extend over eastern and southern Europe, Africa, the Middle East (including Israel), Russia, and western and south Asia (especially India). The natural life cycle of the virus includes certain species of female mosquitoes as vectors with birds serving as the primary vertebrate hosts that replicate the virus to high titer (amplifying hosts). Humans and other mammals (particularly horses) are incidental hosts with transmission occurring through bites of infected mosquitoes. Peak transmission occurs in the late summer and early fall.

There were no cases of WNV infection in North America (or the entire Western Hemisphere) prior to a WNV outbreak in New York City in summer 1999 (101). The virus then became dormant during the winter months but reemerged to cause a small number of human cases during the summers of 2000 and 2001. However, a much larger epidemic occurred in the U.S. in 2002, with significant geographic spread, including westward migration. Over 4,000 cases and 284 deaths were reported that year in 40 states (102).

The possibility of WNV transmission by transfusion was not unexpected, given that asymptomatic WNV infection is associated with a brief, up to 2-week period of viremia (103). Blood donors, as most of the population, are susceptible to this infection which had not been encountered on a large scale previously in the U.S. A total of 23 transfusion-transmitted WNV infection were confirmed in the summer and fall of 2002, including a case of WNV transmission from an organ donor to four recipients where the organ donor was likely infected by one of over 60 transfusions given prior to organ harvest (103,104). In approximately half of the transfusion-transmitted cases the recipients developed meningoencephalitis and several died. The severity of infection appeared to be to a large degree dependent on the recipient age and health status, with more severe outcomes seen in older immunocompromised patients. All types of blood components (red blood cells, platelets, and fresh frozen plasma) were implicated in transmission.

FDA and blood collection organizations took a number of actions to lower the risk of transfusion-transmission of WNV (103). Policies for management of donors with proven or suspected WNV infection were implemented, along with policies for product quarantine, product retrieval, and notification of transfusion recipients. In December 2002, a recommendation was made to voluntarily withdraw selected frozen products from hospital and blood center inventories collected during the 2002 mosquito-borne transmission season in areas of the country that had documented mosquito-borne transmission of WNV to humans.

Blood donor screening with NAT assays was implemented throughout the U.S. in early summer 2003, just prior to the start of the year's main mosquito season. From late June 2003 to December 2003, approximately 6 million donations were screened for WNV, yielding over 800 (0.01%) viremic donations (Fig. 11.2) (105). The majority of WNV-positive blood donations originated in central western states of the U.S., consistent with the predicted westward migration of the outbreak.

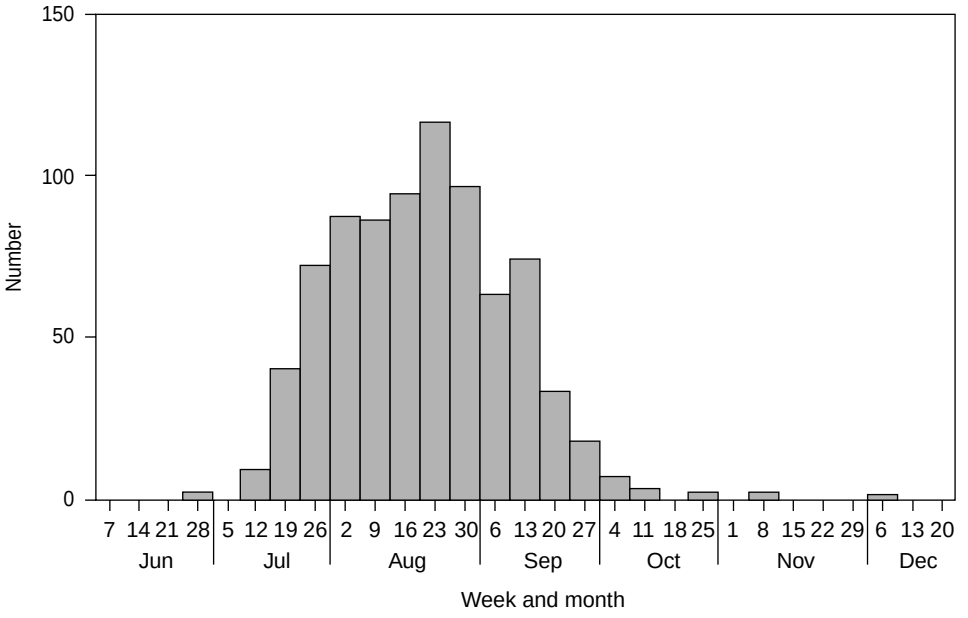


Figure 11.2 Number (N = 818) of U.S. blood donors with presumed viremic WNV infection by week of donation from June 2003 to December 2003. (Adapted from Centers for Disease Control and Prevention [CDC]. Update: West Nile virus screening of blood donations and transfusion-associated transmission—United States, 2003. *MMWR Morb Mortal Wkly Rep.* 2004;53(13):281–284.)

Like in HIV and HCV blood donation NAT screening, for logistical reasons samples were tested for WNV RNA using minipools containing plasma from 6 to 16 donors (MP-NAT), thus lowering the sensitivity of the WNV NAT assay and potentially allowing for breakthrough transmissions by units with low level viremia. Six cases of confirmed or probable transfusion-transmitted WNV were documented in 2003, and data suggest there may have been as many as 50 to 100 additional MP-NAT breakthrough transmissions (105). The median age of the recipients with documented infections was 63 (range 13 to 82); four had WNV encephalitis, one had West Nile fever, and one critically ill patient did not have discernible WNV-compatible illness despite confirmed WNV infection. Each had received multiple blood components, including single infectious units collected during the summer months of 2003. The presumptive transmitting donations were nonreactive by pooled screening, but tested positive upon retrospective testing on an archived undiluted sample, demonstrating the capability of WNV to be transmitted by transfusion at low levels (estimated median viremia from 4 of the 6 transmission cases was 0.11 plaque-forming units per mL). None of the donors reported WNV illness before or after donation. The documentation of these breakthrough infections led to implementation of strategies for conversion from MP-NAT to single donation NAT in collection regions with high WNV activity, as evidenced by clinical case reporting or MP-NAT yield rates. This targeted ID-NAT strategy proved highly effective in 2004 (106,107).

Another member of the Flaviviridae family, also transmitted to humans by the bite of an infected mosquito, is the dengue fever virus (108). The clinical syndrome most often caused by dengue is an acute flulike illness; meningoencephalitis is rare. The rarer, more severe complications of dengue are thought to require an initial infection with one strain of the virus and a second infection with a different strain. Dengue is widespread in tropical regions of the world including Central and South America and the Caribbean islands. The number of cases in these regions has increased over the last several decades. Cases of dengue fever are rare in the U.S. and Canada and there is no evidence of local mosquito-borne transmission in this part of the continent.

To date, no well-documented transfusion-transmitted cases of Dengue have been reported anywhere in the world. Nevertheless, transfusion-transmission of arboviruses other than WNV, in the U.S. most likely eastern equine encephalitis (EEE), western equine encephalitis (WEE), St. Louis encephalitis (SLE), and La Crosse (LAC) encephalitis (108), may be expected, since, in most people, there is an acute viremia of a few days to perhaps 2 weeks following exposure and preceding symptom onset (in the minority of patients that develop symptoms).

NEW AND EMERGING VIRUSES

Recent recognition of West Nile Virus as a transfusion-transmissible infectious agent has focused renewed attention

on emerging infections in transfusion medicine (109). Of particular concern are animal viruses that cross species barriers and cause new infections in humans (so-called zoonoses). Several of these have recently caused highly publicized outbreaks of communicable diseases in humans, including severe acute respiratory syndrome (SARS) (110), monkey pox infection (111), and avian influenza A (112). Another group, cell-associated so-called foamy viruses are frequently found in nonhuman primates, but also cats and cows. Simian foamy virus (SFV) has been isolated from humans, including blood donors, who likely acquired them from animal sources (113–115). While SFV infections are not considered pathogenic and only a fraction of zoonotic viruses cause symptomatic disease in humans, the general lack of immunity in the human population at large creates the potential for devastating pandemics such as occurred in past global outbreaks of influenza (116) and the ongoing AIDS pandemic. None of the viruses considered here are blood-borne organisms in the classical sense, and are therefore not likely to be transmitted by transfusion to any significant extent. Nevertheless, episodes of viremia have been documented in SARS (117), prompting temporary prophylactic deferral of blood donors exposed to the disease. SARS is probably not unusual in this respect, and it can be assumed that periods of asymptomatic viremia also occur with other zoonotic infections that cause disease outbreaks in humans. An additional potential threat is that zoonotic viruses may acquire new mutations as they adapt to the human host, which could change their mode of transmission and alter other properties that could increase transmissibility and pathogenicity in general (118).

Another source of possible new transfusion-transmitted viruses are well-known human viruses that cause common communicable diseases such as enteroviruses. While infection is usually asymptomatic or causes mild and self-limited diseases in healthy adults, severe symptoms may ensue in vulnerable populations such as infants, immunosuppressed patients, and the elderly. Researchers in Scotland have identified seasonally fluctuating viremia involving enterovirus species in approximately 1 in 4,000 Scottish blood donors (119). The significance of this finding for disease transmission and the need for routine donor screening and other preventive measures to protect the blood supply have not been established yet, but are obvious areas for further investigation.

BACTERIAL CONTAMINATION

Bacterial contamination of blood components, which may result in potentially lethal septic reactions in transfusion recipients, has been a well-recognized threat to transfusion recipients since the beginning of transfusion therapy (120). There is no indication that bacterial contamination is on the rise, per se, but continuous increase in the use of platelets (121), the blood component associated with the vast majority of septic reactions, has resulted in an increase in documented septic transfusion reactions and greater awareness of this complication. Prior to recent implementation of testing (see below), bacterial sepsis was the number one cause of acute transfusion-related mortality linked to an infectious agent.

The risk of septic reactions, classically characterized by fever, chills, and rigors, potentially progressing to septic shock, is far greater with platelets than with red blood cells and other blood components. The main reason is the required room temperature storage of platelets which, despite restriction of storage length to 5 days, provides far better growth potential for bacteria than occurs with refrigerated red blood cell storage for 42 days.

The incidence of bacterial contamination in allogeneic blood components, as determined by culture methods, has been estimated as approximately 1 in 3,000 for platelets and 1 in 30,000 for red cells (122). In a recent 2-year national U.S. study, serious septic reactions, including death in nearly a third of confirmed cases, were reported in approximately 1 in 100,000 platelet transfusions and 1 in 5 million red cell unit transfusions (123). Due to lack of clinical awareness and underreporting, these figures undoubtedly represent a low estimate (128).

Micro-organisms isolated from contaminated red cell units include *Staphylococcus epidermidis, Serratia liquefaciens, Pseudomonas* species, and *Yersinia enterocolitica*. The latter, a gram-negative endotoxin producing organism is remarkable for its preference to grow at colder temperature in iron-enriched environments. Gram-positive skin saprophytes account for most of the organisms contaminating platelet concentrates, with the remaining cases attributed to gram-negative organisms associated with occult bacteremia. Most fatal reactions are due to endotoxin reactions associated with gram-negative bacteria. Platelet concentrates contaminated with *Bacillus* species, *Escherichia coli, Klebsiella species, Staphylococcus aureus, S. epidermidis, Serratia marcescens*, and *Streptococcus* species account for 85% of fatal reactions (124). Moreover, although the bacterial content in a contaminated component at the time of collection may be exceedingly small, bacteria propagate during component storage (unlike viruses) resulting in a many log increase in concentration and release of endotoxin and other toxic metabolites. The minimal bacterial doses in platelet concentrates leading to morbidity or mortality are not known precisely. However, bacterial concentrations of 10^8 CFU per mL have consistently resulted in fatalities (125).

Until recently, prevention of bacterial contamination of blood products has relied on selection of healthy blood

donors and adherence to strict aseptic techniques at likely entry points of bacteria such as blood donation, component preparation, transport, storage, and infusion. In a determined attempt to further reduce bacterial contamination and septic transfusion reactions, U.S. blood centers and transfusion services implemented systems for detection and limitation of bacterial contamination in platelets in early 2004 (126). Most detection systems require sterile sampling of platelet components 24 hours after phlebotomy to allow viable bacteria to propagate to detectable levels. Approximately 4 to 10 mL samples of the platelet component are inoculated into automated culture systems, where bacteria are detected through evidence of oxygen consumption or carbon dioxide generation in plasma or enriched growth media. Though generally successful, these methods have natural limitations due to slow growth rates and lack of easily detectable metabolic products in some pathogenic bacteria.

Several nonculture bacterial detection systems have also been described and are under development, but their sensitivity and/or specificity have not as yet achieved those of culture methods (120). Finally, more effective prevention of bacterial contamination can be achieved by the use of newer skin disinfection solutions during donor phlebotomy, and by diversion and discard of the first 15 mL of collected blood (which is then used for blood typing and infectious disease screening). These methods alone or in combination may reduce the bacterial load in skin fragments trapped in the phlebotomy needle that subsequently enter blood storage containers (127,128).

The outlined measures aimed at reducing bacterial contamination of blood components are likely to have a significant positive impact on septic transfusion reactions. Concerns are being raised however about unwelcome consequences of these efforts. Namely significant increases in costs and more frequent platelet shortages due to higher discard rates and shorter windows during which platelets are available for distribution. It is possible that evidence of lower bacterial contamination rates attributable to the new safeguards will permit return to a 7-day platelet storage period, as was the case before rising rates of septic reactions in the 1980s forced implementation of the current 5-day storage period. A longer distribution period for platelets could at least partially offset financial losses and raise the availability of this essential blood component (124). However, longer platelet storage may increase the severity of platelet dysfunction (i.e., storage lesion) associated with the product.

Spirochetes

Serologic tests for syphilis (STS) were introduced for blood screening in the United States in 1938 and were required by regulation in 1958. The last case of documented transfusion-transmitted syphilis in the U.S. was reported in 1966 (1). Treponema pallidum, the spirochete causing syphilis, loses viability after 5 days of storage at refrigerated temperatures. Experiments to determine viability following storage at room temperature have not been performed. The concomitant administration of antibiotics to some patients receiving transfusions probably decreases the occurrence of transfusion-associated syphilis.

The absence of documented cases of transfusion-transmitted syphilis and low viability of the organism *ex vivo* have led to debate over the need for continued donor screening. The main argument for continuing screening of blood donors for syphilis has been that STS may serve as a surrogate test for HIV or other pathogens. But even before implementation of HIV NAT, the number of HIV antibody-negative and antigen-negative cases detected by STS was negligible (129), and the value of STS for this purpose can be expected to have further declined since then.

Tick-borne Bacteria

Ticks are increasingly recognized important vectors of bacterial zoonoses; examples of infections transmitted to humans include Lyme disease, ehrlichioses, and rickettsioses (130). Reports of tick-borne diseases, which also include viral and parasitic infections, among them Babesiosis which is discussed under parasites below, rose sharply in the U.S. in recent years (131,132). This may be in part due to newly instituted reporting requirements of tick-borne infections to state health agencies, but one can speculate that there is also a true increase caused by factors such as a widening geographic range of tick vectors in the U.S., spread of residential areas to tick habitats, and increasing popularity of outdoor sports and leisure activities that bring humans in contact with the vector.

Lyme disease, caused by the spirochete *Borrelia burgdorferi*, is the most common vector-borne illness in the U.S., with more than 23,000 infections in 2002 (133). The disease is transmitted to humans by bites from infected ticks of the species *Ixodes scapularis* or *pacificus*. Spirochetemia likely occurs postinfection and may be present in asymptomatic persons, raising concerns regarding infection in donors in endemic regions. Nonetheless, no clinical or serologic evidence of transfusion-transmitted Lyme disease was demonstrated in cardiothoracic surgery patients receiving blood collected in New England during the peak deer tick season (134), and to date there have been no confirmed reports of transfusion-acquired Lyme disease (132).

Other tick-borne pathogens that may be transmitted by transfusion include *Rickettsia rickettsii*, the causative organism of Rocky Mountain spotted fever (RMSF) and *Anaplasma phagocytophilum* (formerly *Ehrlichia* species), the agent

responsible for human granulocytic ehrlichiosis (HGE), an acute febrile illness similar to RMSF but without the characteristic petechial rash. Single cases of transfusion transmitted RMSF and HGE were reported in the late 1970s and 1990s, respectively (132). In both cases the transmitting blood units had not been leukocyte-reduced. Since the causative agents are obligatory intracellular bacteria, recent widespread adoption of leukocyte reduction of cellular blood components can be expected to have lowered the risk of transfusion transmission of these organisms (135).

PARASITES

A variety of parasitic infections are transmissible by transfusion, most commonly malaria, Chagas disease, and babesiosis which are discussed in greater detail below. Rare cases of transfusion-transmitted trypanosomiasis (African sleeping sickness), leishmaniasis, toxoplasmosis, and microfilariasis have also been reported, primarily in areas endemic for these organisms (136,137). Transmission of parasites through blood products is a particular concern in resource poor, tropical and subtropical countries, where a significant proportion of prospective blood donors are afflicted and transfusion of fresh whole blood is standard practice, but occasional cases of transfusion-transmitted parasitoses are also encountered in the U.S. and other industrialized nations.

Plasmodium Species (Malaria)

In the United States, malaria occurs in travelers, military personnel, and immigrants from endemic countries. Occasional cases result from mosquito transmission, blood transfusion, or organ transplantation. Approximately three transfusion-associated malaria cases occur per year in the U.S. with a reported incidence of 0 to 0.2 cases per million units transfused during the 5-year period from 1993 to 1998 (138). Malarial parasites, *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*, maintain viability in red blood cells (RBCs) stored at 4°C, in platelet concentrates stored at room temperature, and following RBC cryopreservation and thawing. Malaria is not transmitted by RBC-free components such as fresh frozen plasma and cryoprecipitate.

The clinical presentation of malaria (mosquito-transmitted or transfusion-transmitted) includes chills, fever, and splenomegaly. Fatigue, nausea, vomiting, headache, and diarrhea may also occur. Anemia may be severe with associated hemoglobinemia and hemoglobinuria, especially with *P. falciparum* infection. Glucose-6-phosphate dehydrogenase-deficient RBC are resistant to malaria. Persons lacking Duffy RBC antigens are refractory to *P. vivax* infection (139). Patients with sickle cell trait have partial resistance to *P. falciparum*. Babesiosis (see below) should be considered in the differential diagnosis.

In endemic countries, where the vast majority of donors and recipients have been previously infected, all recipients are administered inexpensive prophylactic medication prior to transfusion. Prevention of transfusion-transmitted malaria in non-endemic countries currently relies on deferral of blood donors emigrating or returning from malaria endemic regions, an imperfect strategy that misses some infected donors and excludes many from donation that are not infected. Currently available laboratory tests are not helpful in most blood donor screening settings, as they are either impractical, insensitive, or too nonspecific to be useful for blood donor screening. Experimental assays for combined detection of antimalarial antibodies and antigens (140) or detection of DNA by NAT (141) are under evaluation in several countries with large immigrant populations from regions with endemic malaria (e.g., Great Britain); preliminary data suggest that these tests may prove useful in the future.

Babesia Species

Babesiosis is a malarialike zoonosis in which humans are infected incidentally, usually through the bite of an infected tick of the genus *Ixodes*. Most cases of human babesiosis in North America are caused by *Babesia microti*; the predominant species in Europe is *B. divergens*. Babesia infections are usually asymptomatic or associated with mild flulike symptoms. However, immunocompromised individuals are at risk for life-threatening disease (142). Endemic to the Northeastern and upper Midwestern U.S., the disease is more recently recognized in Eastern and Western regions of the nation as well (143,144). More than 40 cases of transfusion-transmitted babesiosis associated with either red blood cell or platelet transfusions have been reported in the U.S. since 1980 (145). Persons with a history of babesiosis are indefinitely deferred from donating blood, but no blood donor screening test or other effective means exist currently to detect asymptomatic carriers of the parasite (132,145,146).

Trypanosoma (Chagas Disease)

American trypanosomiasis or Chagas disease was named after the Brazilian physician Carlos Chagas who was the first to describe the disease in 1909. There is a generally asymptomatic or mild, self-limiting acute illness, followed by a chronic phase marked by cardiac disease, megacolon,

or achalasia that occurs in up to 30% to 40% of infected patients after a long latency period (147).

The etiologic agent of Chagas disease is the flagellate protozoan parasite, *Trypanosoma cruzi*. The infection is limited to the western hemisphere where it is widespread in Latin America from Mexico to the lower half of the South American continent. Humans become infected through bites from *T. cruzi*-infected insects of the *Reduviidae* family (kissing bugs). Efforts to eradicate the vector have resulted in a decrease of new infections in endemic areas. Infected persons maintain a low level, intermittent parasitemia that usually persists for life; treatment is only effective in eradicating the parasite when rendered during the initial acute stage. Vector transmission is unlikely outside endemic areas, but 50,000 to 100,000 infected Latin American immigrants reside in the U.S. and congenital transmission may contribute to the reservoir of infected persons among immigrant communities (148). At least six transfusion-associated cases of Chagas disease have been reported in immunocompromised patients in the U.S. and Canada since 1989; in all cases the implicated donors were *T. cruzi*-infected Latin American immigrants, and in five of the six cases platelets appeared to be the transmitting component (149). The low number of confirmed cases of transfusion transmitted Chagas disease in North America may be misleading, since they involved fulminant disease in immunosuppressed patients, suggesting that transmissions in immunocompetent recipients, who may have asymptomatic or mild acute disease, may be overlooked.

The prevalence of *T. cruzi* infection among U.S. blood donors varies widely. Nationwide estimates suggest a rate of 1 in 25,000 donors, while communities with a large Latin American immigrant population have 3 to 4 times higher rates (149,150). The parasite may survive 2 to 3 weeks of cold storage and cryopreservation in blood components (136), but the risk of transmission of *T. cruzi* from seropositive donors residing in the U.S. appears to be low probably because the frequency and level of circulating organisms are low decades following the initial infection. In one survey none of the 18 recipients who received blood from a seropositive donor and who were available for testing, had evidence of infection (149). Nevertheless, transfusion-transmitted Chagas disease is seen as a rising concern in the U.S., and universal screening for infected blood donations may be implemented once suitable screening and confirmatory assays are licensed.

Experience from South America where blood donors are routinely screened with tests for antibodies against *T. cruzi* antigens demonstrate the lack of satisfactory sensitivity and specificity of current antibody tests, but suggest that improved performance may be achieved with newer multi-antigen assays (151). Pathogen reduction methods with psoralens (152) or other agents, and to a lesser degree leukocyte reduction of cellular blood components (152,153), offer alternative approaches to reduce transfusion transmission of the parasite. Leukocyte reduction, which appears to be only 40% to 50% effective, has been widely adopted in North America and Europe, unrelated to its effect on transmission of *T. cruzi*. Reliable pathogen reduction methods are still essentially limited to plasma products, with methods for treatment of platelet and red cell components in clinical trials (154,155).

Prions (Classical and Variant CJD)

Classical Creutzfeldt-Jakob disease (CJD) is a rare, fatal, degenerative neurological disease with a long asymptomatic latent period that was first described in 1920. The etiologic agent of CJD is thought by most experts to be a prion protein (PrPsc), an abnormal conformation of a normal cellular protein (PrPc) that can induce conformational transformation (recruitment) of additional PrPc to PrPsc, resulting in deposition of insoluble precipitates in neural tissue and progressive dementia (156). CJD is one of a variety of prion diseases of humans that occur spontaneously at a rate of about 1 per million throughout the world, or can be transmitted vertically in familial conditions such as Gerstmann-Straussler-Scheinker syndrome (GSS), or horizontally through ritualistic cannibalism (kuru).

There are no reported cases of transmission of classical CJD by blood transfusion. Nevertheless, due to the long incubation phase of the disease (as demonstrated from contaminated growth hormone transmissions) concern arose in the mid 1990s that CJD transmission could occur from asymptomatic donors to blood transfusion recipients (157). This theoretical risk led to the establishment of donor deferral policies (based on iatrogenic exposure or family history of the disease) for potential CJD carriers. Several recent epidemiologic studies have confirmed earlier studies in failing to establish a link between transfusion and transmission of CJD (157). Although still regarded as a theoretical risk, there is an emerging consensus that classical CJD is not transmitted by transfusion.

Like classical CJD, variant CJD (vCJD) is a fatal, degenerative neurological disease, although it occurs in younger persons and has distinctive epidemiological, clinical, histopathological, and biochemical features, including the presence of readily detectable prion protein in non-CNS lymphoreticular tissues such as appendix, spleen, tonsil, and lymph nodes. In contrast to classical CJD, vCJD disease is new, with the first reports from the United Kingdom (UK) occurring in 1996 (158). Over the first several years of investigation, it was proven that the etiologic agent of vCJD (also probably a prion) is the same agent that causes bovine

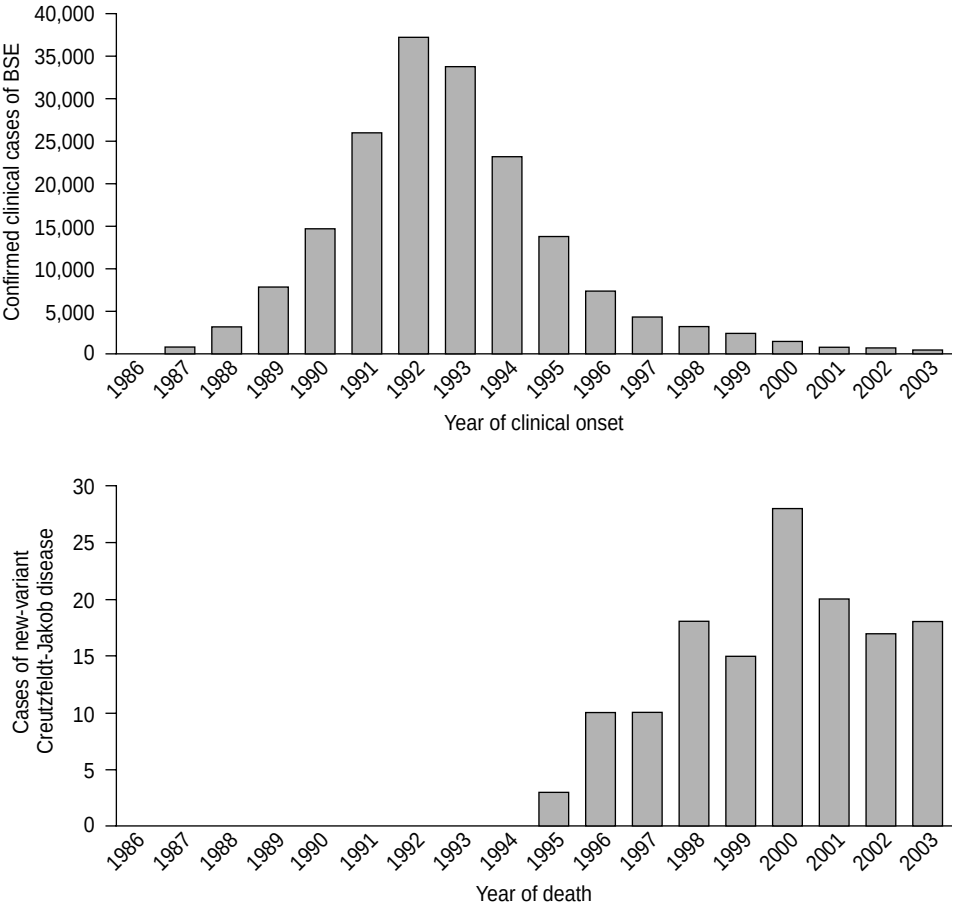


Figure 11.3 Shown are the numbers of confirmed cases of bovine spongiform encephalopathy (BSE, top) vis-à-vis numbers of clinical cases of new variant Creutzfeldt Jakob disease (vCJD, bottom) from 1986 to 2003 in Great Britain. The epidemic of BSE in Britain peaked in 1992, 4 years after the introduction of the ban on feeding tissues of one ruminant animal to other ruminant animals. First cases of the associated human disease, vCJD, appeared several years after the onset of the BSE epidemic. The incidence of vCJD cases appears to be leveling off after reaching their maximum in 2000, hopefully following the same trend as BSE cases in Britain. If so, the concern about transfusion-transmitted vCJD should decline as well. (Reprinted with permission from Donnelly CA. Bovine spongiform encephalopathy in the United States—an epidemiologist's view. *N Engl J Med.* 2004;350(6): 539–542.)

spongiform encephalopathy (BSE). A massive epidemic of BSE occurred in Great Britain in the 1980s and early 1990s, due to the recycling and processing of material (offal) from dead sheep and cattle into food meal for cattle. Although this practice was stopped in the mid 1990s following appreciation of the BSE epidemic, an estimated 250,000 cattle had already been infected with BSE. Transmission of the BSE prions to humans occurred by oral consumption of beef and other cattle products containing reticular endothelial (RE) or neural tissue, resulting in a delayed outbreak of vCJD in the UK (Fig. 11.3).

Several observations raised the theoretical concern that vCJD could possibly be spread by blood transfusion. These included (a) the unknown but potentially large reservoir of asymptomatic carriers of vCJD in the UK and other countries with significant imports of UK beef products, (b) the possibility of a long incubation period as has been observed with other transmissible spongiform encephalopathies, (c) the detection of the vCJD prion protein in lymphoid and other RE cells (dendritic cells), (d) the biological differences between the prions and pathogenesis vCJD and classical CJD which make it unreasonable to extrapolate epidemiological data about the lack of transfusion-transmission of classical CJD to vCJD, and (e) studies using rodent and primate animal models that demonstrated infectivity in blood and implicated transfusion as a possible mode of transmission (159).

Based on the concern that vCJD could theoretically be transmitted by blood transfusion and the finding that initially all known cases of vCJD could be traced to time spent in the UK, a policy was adopted in 1999 of indefinite deferral of persons who spent more than 6 months in the UK from 1980 to 1996 (160). The prediction was that this would reduce the number of donors potentially infected with vCJD by about 70% and would result in the deferral of about 2.5% of otherwise eligible donors. Following discovery of vCJD cases in continental Europe, the deferral policy was revised to include donors if they had spent more than 3 months in the UK or 5 years in Europe since 1980 (160).

As of July 2004, 147 definite or probable cases of vCJD have been reported in the UK (161) with an additional six cases originating in France and one in Italy. Four additional reported cases have occurred elsewhere (one each in

Canada, the U.S. (162), Hong Kong, and Ireland) but these infections were likely acquired in the UK. There have been no significant changes in vCJD epidemiology other than that the potential rate increase of vCJD in the UK that had been predicted by early worst-case models did not occur, and in fact the disease attack rate has declined progressively since a peak in 2001.

The possibility that vCJD may be transmitted by transfusion received new attention following the recent report of the disease in a transfusion recipient who had received one red cell component from a blood donor who died of vCJD 3 years after the donation (163). The implicated donor was one of 15 identified in late 2003 from a total of then 145 vCJD cases on Britain's national CJD surveillance unit register. The recipient became ill 6 years after the transfusion and died of vCJD 13 months from onset of symptoms. The diagnosis was confirmed by examination of brain tissue. Statistical analysis suggests it is unlikely that the recipient acquired vCJD unrelated to the transfusion, and a second case of apparent vCJD transmission reported in Britain in the summer of 2004 provides additional support for the concern that the disease can indeed be transmitted by transfusion.

In estimating the risk of transmissibility of vCJD by transfusion it should be emphasized that the mentioned reports are so far the only cases that suggest a direct link. To date none of the at least 47 other recipients of blood components donated by the 15 individuals with vCJD in the UK registry have been diagnosed with the disease, and the donors who provided blood for four transfusion recipients that were later diagnosed with vCJD are all well (163). It is perhaps also encouraging that the eventual total number of vCJD cases are declining with recent reports projecting a range of 205 to several thousand total cases. However, such estimates are critically dependent upon the nonquantifiable assumptions that underlie them (164).

INFECTIOUS RISK OF AUTOLOGOUS TRANSFUSION

Interest in autologous transfusion increased dramatically in the 1980s, largely driven by the concern over transfusion acquired HIV, then leveled off and decreased over the last decade, paralleling vast improvements in blood safety with regard to viral transmission. This is reflected in the proportion of autologous blood units collected in the U.S. during this period, which increased almost 30-fold from 0.3% of all units collected in 1980 to a peak of 8.5% in 1992, and subsequently declined to just under 5% in 2000 (165).

While autologous transfusion is the safest option for elective surgical patients who are concerned about infection with exogenous viruses, the same is not true for bacterial contamination. Although bacterial sepsis is a rare event in autologous donor–patients and has not been extensively studied, it appears that the rates of bacterial contamination and transfusion-related bacterial sepsis are generally higher than in allogeneic transfusion (166,167). Contributing factors are greater likelihood of underlying medical conditions in autologous donor–patients that predispose to unrecognized bacteremia, application of less stringent donor selection criteria which place greater emphasis on allowing candidates for autologous donation to be accepted as donors, and often maximum length of blood storage before transfusion which increases the growth potential of contaminating bacteria. Standards for qualification of autologous donors recognize this risk and specify that donor–patients who have a clinical condition for which there is a risk of bacteremia shall be deferred from donation (168). The ordering physician and the medical director of the collecting facility have joint responsibility in considering the increased likelihood of bacterial contamination in autologous donation and in addressing this concern as appropriate.

Specific federal rules apply to infectious disease testing of autologous units and notification of donor–patients and hospital staff in cases with positive test results. Autologous units that are transfused outside the collection facility must be tested with the same infectious disease marker assays that are required for allogenic blood donations. If significant positive results are obtained, the patient's physician, the patient, and the receiving facility must be informed. A controversial issue is whether transfusing facilities have the right to refuse acceptance of autologous units that tested positive for infectious disease markers. Since asymptomatic HIV infection has been recognized as a qualifying condition under the Americans with Disabilities Act (ADA), it can be argued that not accommodating HIV-infected persons who wish to donate and receive autologous blood might constitute a violation of the ADA. The American Association of Blood Banks has not taken a position on this issue, but strongly recommends that each institution that collects or transfuses autologous blood carefully weigh the implications of restricting or refusing this service (169). Those in favor of accommodating persons with infectious blood to participate in autologous donation and transfusion argue that mandatory precautionary measures that are already in place should protect other patients and staff from accidental exposures. Opponents argue that despite best efforts, accidents and mishaps do happen, as shown in repeated studies where autologous units were transfused to the wrong patient at a low but fairly consistent rate of approximately 1:17,000 to 1:62,000 (170–171). Current risk estimates for HIV and

HCV are significantly lower than these rates, which creates the paradoxical situation that at least in theory some hospital patients would face a greater risk of transfusion-transmitted HIV or HCV infection from receiving an infectious marker-positive autologous unit by mistake, than they would from receiving an infected "window period" allogeneic blood unit. It appears that in clinical practice there is no unified position on this issue. Most blood centers collect autologous blood from infected donors, but hospitals or clinics may restrict acceptance of infectious blood units according to self-assessment of risks and benefits for all parties involved and unique local circumstances.

SUMMARY AND CONCLUSIONS

Implementation of stricter blood donor acceptance criteria, coupled with incremental introduction of sensitive immunoassays and nucleic acid tests dramatically lessened the risk of transfusion-transmitted infectious diseases in resource rich nations over the last two decades. For clinicians and patients in need of transfusion therapy, this is an unequivocally positive development, easing treatment decisions and reducing stress and anxiety when it comes to discussing transfusion options.

Unresolved challenges and concerns remain, however. First, despite the impressive gains in blood safety, transmissions of classically known infectious agents continue, albeit at a much lower level, and new transfusion transmissible pathogens still emerge. This is best exemplified by the current West Nile virus epidemic in the U.S. Second, the costs for further reducing infectious transfusion risks, both in financial terms and in lost blood donations due to false-positive screening test results and precautionary deferrals of donors, are escalating. Whereas serological screening of donors for HBV, HIV, and HCV was essentially cost neutral (i.e., the cost of testing was offset by the savings in prevented infections/disease), the cost for NAT testing exceeds a million dollars per infection prevented or per quality-adjusted life year saved (173). Pathogen reduction methods currently under development promise effective protection from most transfusion-transmitted viruses and other pathogenic organisms, with the exception of prions. These methods are logistically complex, could nearly double the cost of platelet and RBC components, and may adversely impact the efficacy of the transfusion or cause untoward complications in recipients. Blood shortages are likely to worsen because of a declining base of eligible and willing blood donors and extensive restrictions on blood donation, while blood requirements have expanded and utilization is expected to increase into the foreseeable future (121). Finally, blood safety in developing and resource poor nations has not kept up with the advancements in affluent countries, and considerable risks for transfusion-transmitted infectious diseases still exist in many parts of the world (174–178). Such differences in infectious disease transmission contribute to cultural variances in the perception of blood transfusions. For example in sub-Saharan Africa where malaria is endemic, transfusion is often not viewed as a lifesaving therapy.

Answers to these problems do not come easy. Maintaining and hopefully extending the current level of blood safety requires long-term commitment with sufficient financial backing to fund necessary programs and to pay for added costs to the health care system. Given the already high level of blood safety in the U.S. and competing priorities for limited health care funding, it is predictable that new blood safety initiatives will be scrutinized as to their cost–benefit ratio, projected gain over existing procedures and impact on blood availability. While this process may result in rejection or delay of some safety initiatives, it creates the opportunity to adopt rational policy decisions that balance competing needs for a blood supply that is not only safe, but also adequate and affordable. Finally, humanistic principles and epidemiological considerations provide strong arguments in favor of assisting developing countries with the establishment of sustainable blood collection, processing, and transfusion systems (174,177,179). This will benefit not only transfusion recipients in these areas, but will enhance transfusion safety in the U.S. and other affluent countries in the long run. In light of increasing global travel, commerce, and migration, new and emerging infectious agents can traffic from any region of the world to the U.S. overnight. Proactive surveillance through collaborations with blood collection programs in developing countries is a critical barrier to such an event.

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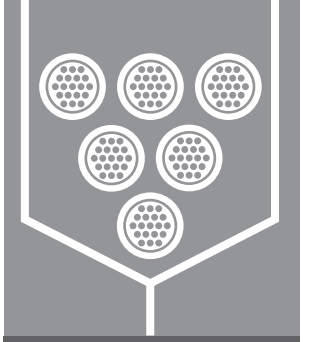

Immunomodulation by Transfusion

12

Neil Blumberg ***Joanna M. Heal***

> It is astonishing how one simple incorrect idea can envelope the subject in a dense fog.
>
> Francis Crick in his autobiography *What Mad Pursuit*, (1,p140).

For the better part of a century, we have known that transfusions evoke immune responses. Humoral immune responses, the formation of antibodies that cause hemolytic disease of the newborn and transfusion reactions, have been known practically since the dawn of the modern era of medicine in the early 20th century. Over the last quarter century it has become clear that transfusion's immunomodulatory effects on cellular immunity are equally important and clinically relevant (2,3). Nonetheless, recent reviews or textbooks that address transfusion immunology largely fail to discuss this subject in any detail because of its controversy and, presumably, a reluctance to embrace ideas that challenge the long-standing assumptions of a successful scientific and clinical enterprise.

Disconcertingly, alteration of cellular immunity by allogeneic transfusions may be of even greater clinical importance than humoral allosensitization (2,3). Some surgeons have long suspected that transfusions are associated with poorer clinical outcomes and most of the initial clinical and scientific work on transfusion immunomodulation is to be found in the surgical literature. A number of reviews of various aspects of transfusion as an immunomodulatory influence have appeared, and the reader is referred to these for a detailed summary of the literature (2,4–7).

The evolving concept of transfusion as an immunodulator of cellular immunity begins with the observations in the late 1960s and early 1970s, that blood transfusions facilitated the acceptance of cadaveric renal allografts (8). This was followed by the still controversial observation that transfusion at the time of cancer surgery was associated with earlier and more frequent recurrences (9,10). It soon became clear that postoperative infections were associated in a dose-dependent fashion with transfusion, (11) and that other diseases of an infectious or immunologic nature were modulated by transfusion, (2) as was the syndrome of repetitive spontaneous abortion during pregnancy (12). Finally, animal models (13,14) and some, but not all randomized clinical trials (15–18) demonstrated that leukoreduction modifies transfusion's immunomodulatory effects.

TRANSFUSION AND HUMORAL ALLOSENSITIZATION

In the late 1940s and early 1950s Billingham et al. published data showing that administration of allogeneic antigen to fetal animals led to tolerance and the science, if not the clinical art of solid organ transplantation began (19). It was some years before the lifesaving promise of kidney allotransplant could be realized, and when it was, the threat of acute allograft rejection due to humoral immunity was recognized. It had been known for decades that transfusion or pregnancy led in many instances to allosensitization to cellular and plasma components of allogeneic blood. Most of the early history of blood transfusion research in the first two thirds of the 20th century was consumed with methods for detecting humoral allosensitization and preventing transfusion of incompatible red cells. Thus until the late 1960s and early 1970s the accepted wisdom was that transfusion stimulated the immune system to make humoral immune responses and that this was the primary immunologic risk to recipients. Two decades later it would become apparent that some antigens, when presented in

large quantity by the intravenous route, are particularly likely to produce a type II (primarily humoral) immune response while down regulating type I (primarily cellular) responses (20–22). Large quantities of antigen, facilitated by the lack of costimulatory inflammatory danger signals can cause outright tolerance in some animal models (23). Approximately 1% to 5% of individuals receiving ABO and Rh (D) identical transfusions or who become pregnant with an Rh compatible fetus will become allosensitized to one of the many polymorphic red cell antigens. Approximately 50% of patients transfused with cellular blood components or who become pregnant will make antibodies to class I histocompatibility antigens present on white blood cells.

By about 1990 or so, methods of preventing posttransfusion allosensitization to white cell antigens (primarily antibodies to HLA class I) became available. Removing most (at least 99%) of the donor white cells using filtration techniques is 90% to 100% effective at preventing de novo primary HLA allosensitizations in patients undergoing myeloablative chemotherapy (24). HLA allosensitization is the primary cause of alloimmune platelet transfusion failure because platelets also carry class I antigens. Platelet transfusion refractoriness secondary to transfusion dropped by an order of magnitude, from about 50% to 5% or less, after the introduction of leukoreduced transfusions (25). Interestingly, it appears that leukocyte reduction by filtration also reduces the immunization rate to red cell alloantigens in patients receiving red cell transfusions (26). One likely contributing mechanism is the removal of the type II immune stimulus caused by the transfusion of allogeneic white blood cells. Purified red cells and platelets are almost certainly less effective immunogens than allogeneic white cells, perhaps because these cells are less efficient at generating an inflammatory stimulus in the recipient that can promote costimulatory molecule activation/expression by the host immune system.

TRANSFUSION AND SOLID ORGAN TRANSPLANTATION

The first inkling that blood transfusions had effects on recipient immunity other than stimulating humoral alloimmunity came from clinical observations in patients receiving cadaveric renal allografts (8,27). The early history of renal transplantation included observations of acute, visually impressive graft rejection during surgery in the case of highly immunized recipients. This immunization was soon linked to previous transfusions. Unfortunately, in the pre-erythropoietin era, the only treatment for the almost universal anemia of renal failure was blood transfusion. The only method of reducing the alloimmunization rate among patients on hemodialysis awaiting transplantation was to reduce the number of leukocytes in the transfused blood, and the only method of doing this was using frozen-thawed red cells that had been cryopreserved using glycerol. These red cell transfusions were leukocyte reduced by about 80% to 90% and plasma and platelet depleted as well. They were modestly effective at reducing the alloimmunization rates seen in transfused patients.

What came as an enormous surprise and was met with complete skepticism was the report that transfused patients actually had reduced rejection and better renal allograft survival than nontransfused patients, an effect that was later seen to be dose-dependent, and not seen in patients receiving leukocyte and plasma reduced blood transfusions (Fig. 12.1) (8,27).

Animal models confirmed the importance of allogeneic leukocytes in mediating this apparent "tolerogenic" effect. In fact, there were some studies (28) suggesting a similar effect could be mediated by platelets, which is of interest in light of recent evidence that platelets and platelet-derived CD40L can stimulate secretion of PGE2 and other down regulators of cellular immunity (29,30). There is also evidence that blood transfusions can facilitate acceptance of heart (31) and liver (32) allografts. Donor-specific transfusions are particularly effective at facilitating engraftment in animal models, but are no longer frequently used in an era in which immunosuppressive agents are highly effective at preventing allograft rejection in most patients.

TRANSFUSION AND CANCER RECURRENCE

The experience with the allograft enhancing effects of blood transfusions, by analogy with the drugs used to prevent rejection, was termed an immunosuppressive effect (33). This raised the question as to whether this effect, beneficial in allograft recipients, might be deleterious in other clinical settings where host cellular immunity might be important. In retrospect, an obvious group of patients who might experience adverse outcomes from transfusion immunosuppression is patients undergoing surgery and/or those with cancer. It was known that patients who were anergic or had reduced delayed hypersensitivity in skin tests were at increased risk of postoperative infections and more likely to have rapid tumor progression.

In the late 1970s it was shown that animals with experimental tumors had more rapidly progressive tumor growth if transfused with allogeneic as opposed to syngeneic blood (34). This would be analogous to the use of allogeneic (homologous) versus autologous clinical transfusions. In 1982, Burrows and Tartter reported that patients in a colorectal cancer trial had dramatically earlier and more frequent recurrences of their tumor if they had been

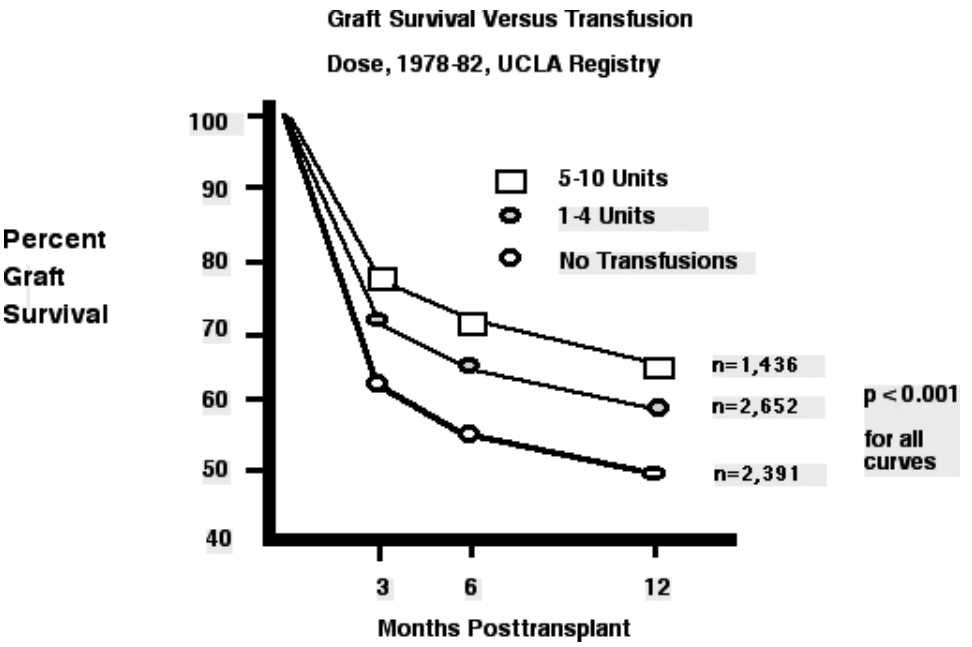

Figure 12.1 The dose response relationship between pretransplant transfusions and one year renal allograft survival in humans is shown from the UCLA registry for transplants performed in the late 1970s and early 1980s. (Adapted with permission from Terasaki PI, ed. *UCLA Tissue Typing Lab*. Cecka M, Toyotome A. The Transfusion Effect. *Clin Transpl*. 1989:335–341. Reprinted with permission from Elsevier. Anderson KC, Ness PM, eds. *Scientific basis of transfusion medicine*. Elsevier; 2000;428.)

transfused at the initial surgical resection (9). Similar observations were made for most other surgically treatable tumors, although about one third of the studies did not achieve statistical significance despite poorer outcomes in the transfused patients (Fig. 12.2) (35–37).

One obvious explanation for the association seen between allogeneic transfusion and earlier tumor recurrence is that the need for transfusion is confounded with size or aggressiveness of the tumor. That is, patients who require transfusions do so in part because they have larger, more

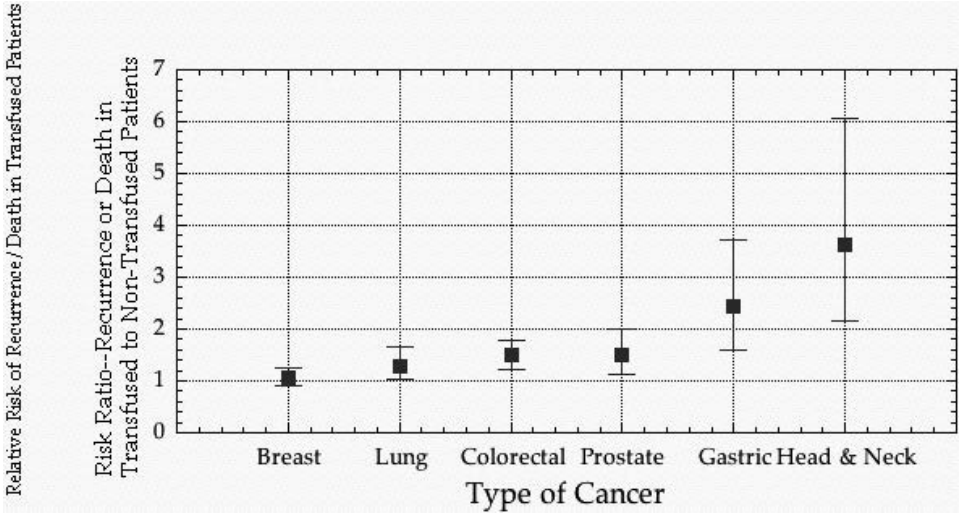

Figure 12.2 The relative risk of cancer recurrence or death in patients receiving allogeneic transfusions versus the risk in those receiving no transfusions is shown for a variety of human cancers, based upon epidemiologic studies. Ninety-five percent confidence intervals of the estimate are shown. A relative risk of 1.0 indicates no additional risk of recurrence or death beyond that seen in nontransfused patients. The relative risk is statistically significantly increased for transfused patients with each tumor with the exception of breast cancer. For comparison, the relative risk for lung cancer in one-pack-a-day cigarette smokers is about 10 compared with nonsmokers, and the relative risk for oral cancer in pipe and cigar smokers is 3.3 compared with nonsmokers. (Data plotted from the meta-analysis results of Vamvakas EC. Perioperative blood transfusion and cancer recurrence: Meta-analysis for explanation. *Transfusion*. 1995;35:760–768. Reprinted with permission from Elsevier. Anderson KC, Ness PM, eds. *Scientific basis of transfusion medicine*. Philadelphia: WB Saunders; 2000;435.)

aggressive, and thus difficult to resect tumors. This certainly accounted for some of the association. However, a number of studies demonstrated that even in cohorts well matched for known prognostic factors, the transfused patients had more frequent or earlier tumor recurrence. Finally, transfusion practice is extraordinarily variable in almost all clinical settings due to the lack of accepted and uniform criteria for initiating transfusion therapy. While transfusion therapy is certainly not given randomly, neither is it given in predictable, consistent fashion. Thus, from first principles, it would be surprising if the twofold to threefold difference seen in tumor recurrence were explained as the product of confounding. In public health research, twofold to three fold differences in outcomes are usually causal in some degree (38,39).

At the time these studies were appearing in the 1980s, the concept that the immune system was critical in tumor outcomes was falling out of fashion because of failures of treatments such as interferon and BCG vaccination, which had shown promise in animal models. Furthermore, immune responses to human tumors had only rarely been demonstrable. The observation that this is probably because successful tumors by definition evade and/or repress host immune responses was still many years in the future (40,41). Thus these early studies were met with significant skepticism, much the way the early studies of the allograft enhancing effects of blood transfusions were.

A number of observations suggested that the association between blood transfusion and tumor recurrence was causal. Firstly, as in the renal transplant data, the type of transfusion made a difference. Whole blood transfusions were associated with worse tumor recurrence rates than were transfusions of equivalent numbers of red cell transfusions that were somewhat depleted of plasma, white cells, and platelets (42–44). In an animal model, removal of allogeneic leukocytes reduced the number of metastases seen after transfusion (13). Use of autologous blood reduced the recurrence rate in patients undergoing colorectal cancer resection in one randomized trial (45) but not another (46). The one study that examined leukocyte reduction as a means of reducing the adverse effects of transfusion showed no benefit (47).

Unfortunately, few large scale trials of leukocyte reduction or autologous transfusions or bloodless medicine and surgery techniques have been mounted in the area of cancer surgery. These are formidable trials to conduct because they require adherence to protocols, large numbers of patients, and long-term follow-up, thus increasing expense and logistic difficulty. Nonetheless, there has been a trend toward decreasing use of transfusion in cancer surgery, (17) largely due to the concerns of the public and practitioners about transfusion transmitted infectious diseases such as HIV and hepatitis C. It is uncertain whether this change in practice has contributed to any improvement in recurrence rates in patients with surgically resectable solid tumors.

With the introduction of universal leukoreduction throughout most of Western Europe and Canada beginning in the late 1990s and early 2000 period, the possibility exists of before and after studies of cancer recurrence, but none have yet appeared. When there is 5 year to 10 year follow-up of patients treated before and after the introduction of universal leukoreduction, there may be some insights into whether leukoreduced transfusions are less immunomodulatory in cancer surgery patients than unmodified transfusions.

TRANSFUSION AND POSTOPERATIVE INFECTION AND MULTIORGAN FAILURE

The association between transfusion and an increased risk of postoperative bacterial infection was first reported by Paul Tartter in the mid 1980s (11,48). Patients transfused preoperatively, intraoperatively, or postoperatively had a several-fold increase in the incidence of infection. This association was confirmed in many other studies, (49) and was not explained by clinical confounders of transfusion such as anemia, blood loss during surgery, duration of surgery, or hypotension. Furthermore, the size of the association was quite large. Patients who receive >10 allogeneic transfusions have an almost order of magnitude increase in their likelihood of developing postoperative infection (50). The effect was seen in a wide variety of surgical settings, including organ allograft recipients receiving immunosuppressive drugs. The effect size is similar in magnitude to that seen in the epidemiologic association between smoking and lung cancer (53), rendering it extraordinarily unlikely to be explained by bias or confounding that are always of concern in observational, cohort studies (Fig. 12.3) (38,39).

Some have argued that a multitude of confounding factors could explain this association (55). This contention is undermined by the relatively unsystematic way in which transfusions are given. In addition the size of the effect argues against a significant role for confounders. That a dose-dependent 10-fold increase in postoperative infections after allogeneic transfusion is solely due to confounders is implausible and unlikely according to epidemiologic principles (38,39).

One problem with some studies is they rely exclusively on culture proven infections, which underestimates the incidence of morbidity, particularly in surgical patients, who routinely receive prophylactic antibiotics. It is necessary to assess morbidity and infection by indirect means

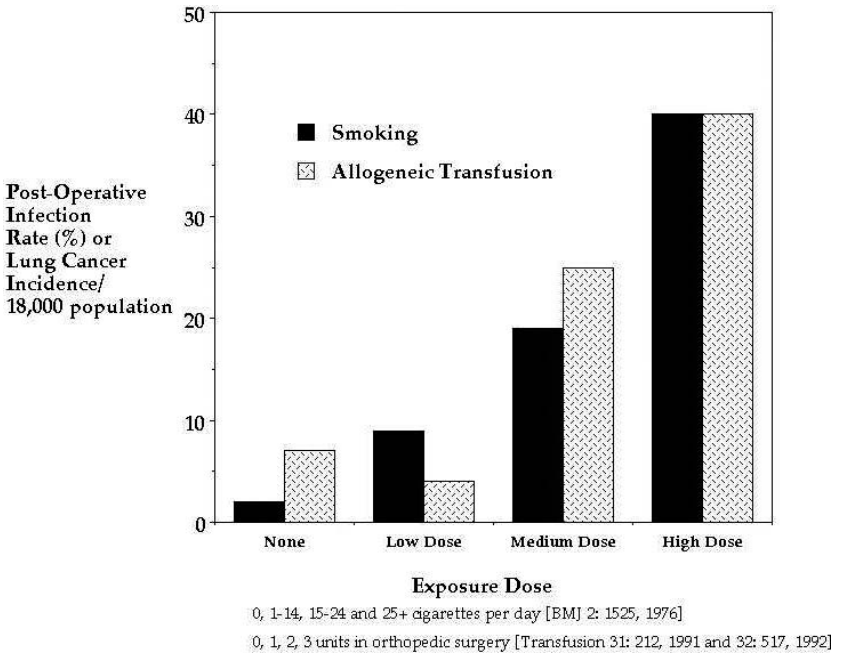

Figure 12.3 The relative risk of postoperative infection according to number of allogeneic transfusions received is compared with the relative risk of lung cancer according to number of cigarettes smoked per day. The 10-fold or greater association of unfavorable outcomes with intensity of exposure to the proposed causal influence provides prima facie likelihood of an underlying cause and effect relationship when "Hill's principles of causation" are considered (dose relationship, size of the effect, underlying plausible mechanism, consistency across studies, benefits of reducing the exposure, etc.). (Adapted from Triulzi DJ, Vanek K, Ryan DH, et al. A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. *Transfusion*. 1992; 32:517–524; Murphy P, Heal JM, Blumberg N. Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusions. *Transfusion*. 1991;31:212–217. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *Br Med J*. 1976;2:1525–1536. Newman TB, Browner WS, Hulley SB. Enhancing causal inference in observational studies. In: Hulley SB, Cummings SR, eds. *Designing clinical research*. Baltimore, Md: Williams & Wilkins; 1988:98–109. Elwood JM. *Causal relationships in medicine*. Oxford, England: Oxford University Press; 1988.)

such as days of antibiotics, length of hospital stay, and signs and symptoms of infection. Other less comprehensive approaches are inadequate. In addition, if transfusion is merely a surrogate marker for clinically unfavorable outcomes, this explanation is incompatible with the observations that transfusion is associated with better, rather than worse, clinical outcomes in patients with inflammatory bowel disease (54) or receiving renal allografts (27). Finally, arguments (55) that introducing a dozen or more supposed confounders makes the association not significant are simply not good statistical methodology or science (56). Only confounders directly and causally linked to both transfusion and infection should be included in statistical models because introduction of irrelevant variables can lead to erroneous acceptance of the null hypothesis in such analyses.

A number of animal models confirmed that this association was likely cause and effect. Alexander, Gianotti, and colleagues demonstrated in mice that allogeneic white cells were much more potent in mediating this effect than red cells or plasma (14). Our group and others found that this relationship between transfusion and postoperative infections was not seen in patients receiving autologous blood, thus confirming the immunologic nature of the effect (Fig. 12.4) (51,52).

The final pieces of evidence proving that the relationship between allogeneic transfusion and increased risk of postoperative infection was causal came from randomized trials of leukoreduced allogeneic transfusions versus unmodified blood, and autologous versus allogeneic transfusion techniques. These studies, to be discussed in greater detail in the last section of this chapter, beyond a reasonable doubt have demonstrated that the incidence of postoperative infection in transfused surgical patients can be reduced by use of leukoreduced blood transfusions, (15–18,47,57–60) or the use of autologous techniques (61). In general, a 50% reduction in postoperative infections is possible using leukoreduced transfusions compared with unmodified red cells.

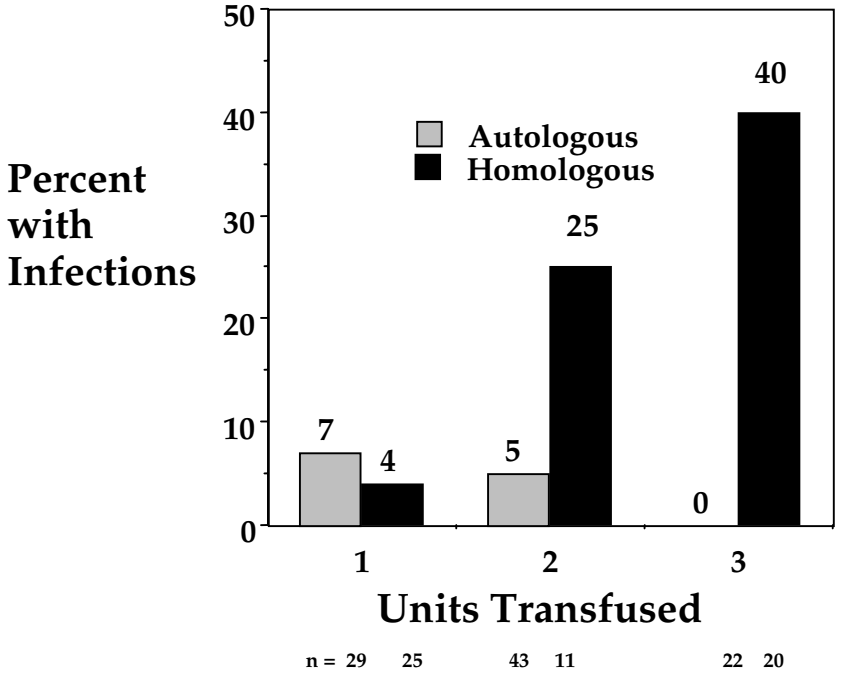

Figure 12.4 Patients undergoing posterior or anterior cervical or lumbar spinal fusion or primary hip replacement surgery, without malignancy, autoimmune diseases, or diabetes were grouped according to whether they had received only autologous blood or only homologous blood. The proportion with culture proven or clinically evident infections, grouped according to number of units of blood transfused is shown. The differences between autologous and homologous recipients are statistically significant at doses of two or three units, but not for one unit of blood. This significant dose-response relationship was also evident when days of antibiotics and length of hospital stay were measured. Infections were predominately away from the wound site: two thirds were cellulitis, urinary tract, or pulmonary. (Data are pooled from Triulzi DJ, Vanek K, Ryan DH, et al. A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. *Transfusion.* 1992;32:517–524; Murphy P, Heal JM, Blumberg N. Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusions. *Transfusion.* 1991;31:212–217. Reprinted with permission from Elsevier. Anderson KC, Ness PM, eds. *Scientific basis of transfusion medicine.* Philadelphia: WB Saunders; 2000;437.)

Recent unpublished evidence from our own center suggests that leukoreduction of blood transfusions reduces the incidence of line related infections in all clinical settings by about 30% to 40% (62).

The association between transfusion and postoperative infection is accompanied by evidence that there is a dose-dependent increase in multiorgan failure syndrome in transfused surgical patients (63–65). This effect could not be explained by confounding factors and has been observed in prospective clinical trials as well. In particular, platelet transfusions have been associated with five-fold excess of postoperative deaths in cardiac surgery after adjustment for other risk factors (66). This large an effect is unlikely to be fully explained by residual confounding (38,39). Furthermore, evidence exists that the association between platelet transfusion and mortality is greatly reduced in patients receiving postoperative aspirin (67). Whether this proposed effect could be mediated by predisposition to infection due to immunomodulation by non-leukoreduced transfusions, (18, 68) a prothrombotic effect of activated platelet transfusions, exacerbation of inflammatory responses from transfused platelet CD40L and sCD40L (29) or all of these, will be subjects of future investigations. Wound healing may also be compromised by allogeneic transfusions (69–71). Once again, from randomized trials and implementation studies it appears that leukoreduction of transfusions may reduce the risk of multiorgan failure in the postoperative period (18) and abrogate the deleterious effect on wound healing (72).

TRANSFUSION AND VIRAL, AUTOIMMUNE, AND GESTATIONAL DISEASES

Given the association between transfusion and postoperative bacterial infection, we hypothesized that allogeneic transfusions might impair host resistance to viral infection.

There is epidemiologic evidence that transfusion accelerates the development of clinical manifestations of HIV-1 infection (73) and CMV infection (74). At least in the late stages of HIV-1 infection, use of leukoreduced blood does not mitigate any effects that might be mediated by transfusion (75). One confounding factor that has become clear in studies of transfusion immunomodulation is that single-center studies are more likely to demonstrate benefits to interventions such as leukoreduction or autologous transfusions. It may be that multicenter studies, which have typically involved a small number of patients at large numbers of hospitals, are less likely than larger single-center studies to detect improvements due to wide variations in other variables that affect clinical outcomes such as infection or survival. The proposed deleterious effects of transfusion on host defenses to virus infection are credible given the effects of transfusion that down regulate immune functions such as natural killer cell activity and macrophage/monocyte cytocidal properties, but are far from proven or accepted.

Given the possible role of viral infections in some lymphoid malignancies in both animals and humans, it is not surprising that allogeneic transfusion in the past is associated with the development of non-Hodgkin's lymphoma, particularly the B cell varieties (76). Not all such studies have found an association. If this association is causal, it is uncertain whether viral transmission or transfusion immunomodulation play a role in this phenomenon, but either or both make mechanistic sense. Transfusion immune modulation causes B cell stimulation through promotion of type 2 (Th2) immunity, and depresses type 1 (Th1) host defenses that may be important in viral immunity and tumor surveillance (Fig. 12.5) (77,78).

There is evidence that transfusion moderates some autoimmune disease processes that are mediated by cellular

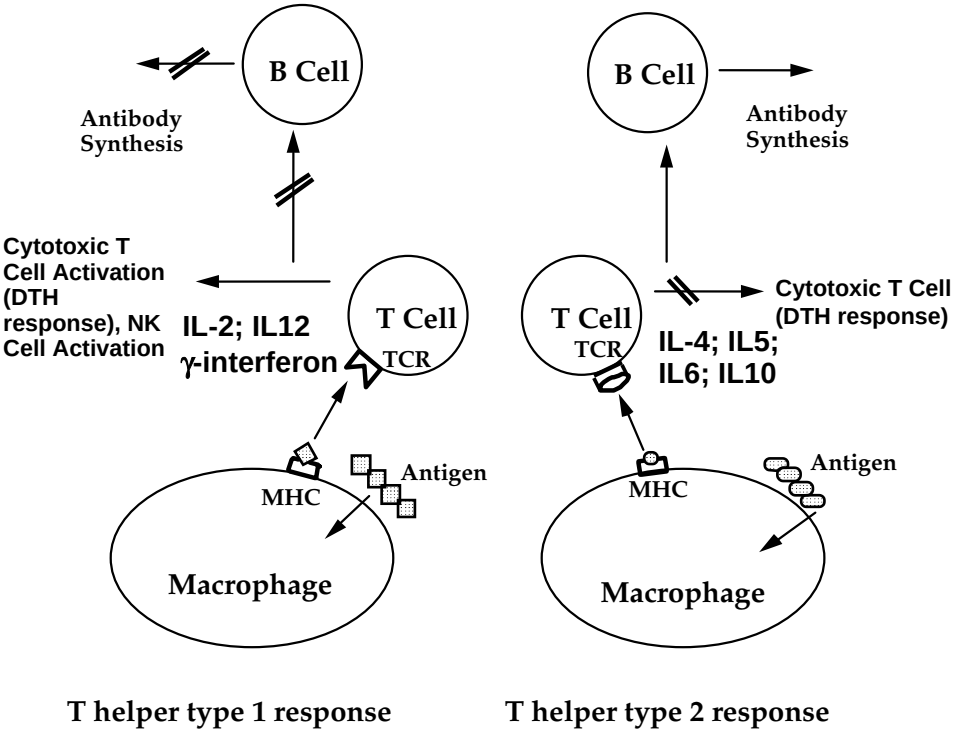

Figure 12.5 A simplified, schematic view of how alloantigens are processed by macrophages and presented to T cells is shown with emphasis on the distinction between responses that primarily involve Th1 or Th2 type cytokines. Similar type I or type II deviated dendritic cells, macrophages and CD8 cytotoxic lymphocytes also have been identified. Allogeneic transfusions appear to evoke primarily type II (Th2) cytokine secretion patterns with reciprocal down regulation of type I (Th1) cytokine secretion. Thus many cellular immune functions are downregulated, including cytotoxic T cell and NK functions. DTH, delayed type hypersensitivity; TCR, T cell antigen receptor; MHC, major histocompatibility complex; NK, natural killer; IL, interleukin. (Adapted from Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today.* 1996;17:138–146. Blumberg N, Heal JM. The transfusion immunomodulation theory: the Th1/Th2 paradigm and an analogy with pregnancy as a unifying mechanism. *Semin Hematol.* 1996;33:329–340. Reprinted with permission from Elsevier. Anderson KC, Ness PM, eds. *Scientific basis of transfusion medicine.* Philadelphia: WB Saunders; 2000;429.)

immunity. These include Crohn's disease (regional enteritis) (54) and rheumatoid arthritis (79). In the case of Crohn's disease, patients with larger sections of affected bowel and more severe disease are more likely to be transfused during surgery for removal of inflamed and damaged small intestine. Nonetheless, transfused patients are less likely or no more likely to have recurrences of their Crohn's disease than nontransfused patients with less extensive and less aggressive initial disease (80). One possible explanation for these observations is a favorable modification of the type 1 auto-immune process by allogeneic transfusion via down regulation of type 1 immunity. Similarly, rheumatoid arthritis involves type 1 immunity and inflammation that in small pilot trials have been favorably affected by infusions of allogeneic white cells (81) or whole blood (79). These observations may be more important as proof of principle that transfusion immunomodulation is clinically significant and operates by down regulation of cellular immunity than as future therapeutic modalities.

One of the earliest observations that transfusion immunomodulates the recipient was evidence that exposure to paternal or third party blood transfusions improved the ability of women affected by repetitive spontaneous abortions to carry a pregnancy to term (12). The effect is relatively small; and different preparations of transfusions yield varied results, but it is undoubtedly real. It is particularly of interest because pregnancy, like allogeneic transfusion, is a state of type 2 immune deviation, with increased expression of cytokines such as IL4, IL5, and IL10 (82). One possible mechanism for the observations in pregnancy is that allogeneic transfusions help down regulate pathologic type 1 immune responses that can lead to spontaneous abortion. Normal pregnancy is characterized by type 2 immune deviation (83) and mildly increased risks of certain intracellular infectious organisms and certain tumors, presumably due to slight decrease in type 1 immune functions needed for optimal immune surveillance. As in transfusion, pregnancy is characterized by a propensity for mounting humoral immune responses as would be expected from a condition of type 2 immune deviation. Of interest to this hypothesis is that red cell transfusions that are leukocyte reduced are less likely to result in alloimmunization not only to white blood cell antigens, but red cell alloantigens as well (26).

MECHANISMS OF TRANSFUSION IMMUNOMODULATION

Transfusion is intravenous administration of relatively large quantities of peripheral blood cells, proteins, lipids, and such diluted with preservatives and anticoagulant. From a practical standpoint, the only natural situations in which the immune system confronts such large quantities of intravenous antigen are, of course, self-antigens, and pregnancy (78,83). Teleologically speaking, these two situations require unresponsiveness or tolerance. To provide defense the immune system has evolved to deal with dangerous foreign antigens (23). These consist primarily of microorganisms, present in small quantities, at mucosal or skin locations, or altered self—tumor cells in small numbers, largely in tissue locations. Therefore, it should not be surprising that large doses of intravenous antigen containing both self-determinants as well as non-self-determinants often results in hyporesponsiveness rather than allosensitization. This appears to be especially true when other influences cause decreased host immune function (e.g., the immaturity of fetal life, surgical stress).

The classic experiments of Billingham demonstrated that exposure during fetal life to foreign tissue could lead to life long acceptance of subsequent skin grafts from the tissue donor (19). Felton found that when pneumococcal antigen was given at high doses, animals were impaired in their subsequent ability to mount a humoral immune response to antigen administered by routes and in doses that invariably cause sensitization ("immune paralysis") (84). In 1951 Kaliss and Snell (85) showed that infusions of various tissue extracts from allogeneic donors prior to tumor implantation accelerated tumor growth in the mouse. Even serum infusion prior to implantation led to death of most of the animals due to tumor growth. The saline infused control animals easily rejected this tumor and survived. Interestingly, of all the tissues extracts infused, only infusions of lyophilized red cells failed to enhance tumor related mortality.

While most studies have focused on the role of transfused allogeneic white cells and their mediators, (86) data have accumulated that stored supernatant plasma may be immunomodulatory (73). Furthermore, it appears that platelets are a rich source of immunomodulatory mediators, such as VEGF, soluble CD40L, and TGF-B1 (29,30,87–90). Platelet-derived mediators such as soluble CD40L are particularly enriched in non-leukoreduced red cell concentrates, whole blood and, obviously, platelet concentrates.

Transfusions from genetically disparate animals of the same species lead to impaired mixed lymphocyte culture reactivity, impaired antigen processing by macrophages, increases in both suppressor cells and humoral suppressive substances, reduction in cell killing, and generation of idiotypic antibodies that can be immunomodulatory in vitro (91,92). This suggests that down regulation of cellular immunity is a vital component to the transfusion effect. Most studies suggest that the presence of white cells in the transfused blood is important to observing the effect, but

evidence exists that plasma, red cells alone, and even purified, soluble class I histocompatibility antigens, or peptide fragments of class I molecules, (93,94) can mediate a similar effect to some degree. That transfusion induced immunomodulation in the transplant setting is at least in part mediated by a PGE2/IL-2 pathway is suggested by data that inhibition of PGE2 by indomethacin or anti-PGE2 antibody blocks this transfusion allograft enhancement effect (95). Furthermore, in another model system, administration of exogenous IL-2 reversed the blood transfusion induced immunomodulatory effect on renal allografting (96). Convincing data show that allogeneic transfusion decreases the ability of mononuclear cells to secrete IL-2 in response to a variety of in vitro stimuli (22,97). Table 12.1 lists most of the immunologic changes that have been demonstrated in studies of animals and patients who have received blood transfusions (78,91,92).

The likelihood that any one mechanism fully explains the effects of transfusion on organ allografts, postoperative infection, tumor recurrence, pregnancy, and autoimmune disease is remote. Nonetheless there are some common mechanisms that may play a role in all of these settings. One recent model for posttransfusion immunomodulation that is receiving attention is shown in Figure 12.5 (20–22,78,97–100). Immune deviation toward secretion of type 2 (T helper type 2;Th2) cytokines (e.g., IL10, IL4) and suppression of type 1 (Th1) cytokines (e.g., γ-interferon, IL2) is one explanation why transfusion impairs recipient immune responses to allogeneic organs, tumors or the fetus. Effective immune responses against tumors and organ allografts may well be Th1 in nature, (101) as is rejection of the fetus as an allograft (82). While this diagram no doubt vastly oversimplifies the detailed biology of such events, it does appear from clinical and animal studies that allogeneic transfusions impair cellular immunity by fostering immune responses that primarily involve IL10, IL4, and TGF-B. These cytokines impair NK and T effector cell functions, some phagocytic cell functions, and generally act as anti-inflammatory mediators. These functions are critical to maintaining antitumor, antiallograft, and antimicrobial immunity, and thus their impairment by allogeneic transfusion provides a reasonable unifying mechanism to explain the altered clinical outcomes that occur.

Surgery without transfusion causes immune deviation toward type 2 (Th2) cytokine secretion which probably contributes to the reductions in cutaneous delayed type hypersensitivity responses seen for the first week or two after surgery (102–104). Whether these effects are due to surgical trauma alone, anesthesia, or other drugs is uncertain. These effects are additive with the effects of transfusion and there are impairments of cellular immunity that last for days to weeks. These effects are not seen, or seen to a lesser degree, in patients receiving only autologous blood (100,103,105) or leukocyte depleted transfusions (15,16,106).

Finally, there is evidence that infusion of apoptotic cells facilitates type 2 immune deviation, (107) organ allograft acceptance (108,109), and multiorgan failure (107) in experimental animals. Apoptotic white cells and platelets, as well as red cells accumulate during blood storage, and are selectively removed by leukocyte reduction filters (110). Thus infusion of storage damaged apoptotic peripheral blood cells may provide the mechanism by which T cell, macrophage, and dendritic cell immunity is biased toward type 2 reactions, and why leukocyte reduction reduces both immunologic and adverse clinical effects (111). While immune deviation greater in intensity but similar in principle to that seen in pregnancy is certainly not the only event that occurs with allogeneic transfusion, it is the one hypothesis that accounts for the broad range of seemingly contradictory clinical findings ranging from reduced spontaneous abortion and autoimmune disease to increased postoperative infection and cancer recurrence. These are shown in Table 12.2.

TABLE 12.1

EFFECTS OF ALLOGENEIC TRANSFUSIONS ON RECIPIENT IMMUNOLOGIC FUNCTIONS

1. Decreased Th1 and increased Th2 cytokine production in vitro.
2. Reduced responses in mixed lymphocyte culture.
3. Decreased proliferative response to mitogens or soluble antigens in vitro; impaired delayed type hypersensitivity skin responses.
4. Increased CD8 T cell number or suppressor function in vitro.
5. Decreased natural killer cell number and activity in vitro.
6. Decreased CD4 helper T cells number.
7. Decreased monocyte/macrophage function in vitro and in vivo.
8. Enhanced production of anti-idiotypic antibodies suppressive of mixed lymphocyte response in vitro.
9. Decreased cell mediated cytotoxicity (LAK) against certain target cells in vitro.
10. Humoral alloimmunization to cell associated and soluble antigens.

(Adapted from Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol Today.* 1996;17: 138–146; Ghio M, Ottonello L, Contini P, et al. Transforming growth factor-beta1 in supernatants from stored red blood cells inhibits neutrophil locomotion. *Blood.* 2003;102:1100–1177; Blumberg N, Heal JM. Transfusion and recipient immune function. *Arch Pathol Lab Med.* 1989;113:246–253.)

Strategies to Modify Transfusion Immunomodulation and Improve Clinical Outcomes

Preventing deleterious effects of transfusion immunomodulation presents a challenge as the precise mechanisms have not been completely worked out. For example, it is not

TABLE 12.2
TH1 PROCESSES IMPAIRED BY TRANSFUSION (AND IN MOST CASES, PREGNANCY)

Solid organ rejection
Tumor rejection
Rejection of the fetus as an allograft
Inflammation of Crohn's disease
Inflammation of rheumatoid arthritis
Inflammation of Type I diabetes (in animals)
Antiviral immunity
Antibacterial immunity

clear whether components other than allogeneic white cells mediate significant effects. However, this seems quite likely. As mentioned, supernatants of platelet concentrates contain significant amounts of the immunomodulatory molecules TGF-B1 and sCD40L that are associated with clinical effects. Platelets themselves express the immunomodulatory costimulatory molecule CD40L. Red cells can express apoptotic levels of phosphatidyl serine that may interact with recipient receptors on immunologically important cells. Cells stored under different conditions for different periods of storage may have different immunomodulatory effects. Clinical data suggest that whole blood has more immunomodulatory potential than red cell concentrates. Whether this is due to differences in platelet content, supernatant plasma, or other variables is unknown at present. It may be that different leukocyte reduction methods vary sufficiently in the residual platelets in the transfusion that this accounts for the heterogeneity of the results seen in clinical studies.

That having been said, there are three reliable ways of mitigating transfusion immunomodulation's deleterious effects. The first is avoiding transfusion through bloodless medicine and surgery practices (112). The second is avoiding or reducing allogeneic transfusions by use of autologous techniques (61). The third is employing leukoreduced (also platelet-reduced as it turns out) red cell transfusions by using high efficiency filters (Fig. 12.6) (15–18,47,57–60,113).

Two randomized trials of autologous versus allogeneic transfusion have yielded divergent results. Heiss and colleagues (45,103) found significant protection against postoperative infection with autologous transfusions and Busch and colleagues (46) reported no such benefit. These are studies with control arms of buffy coat depleted (60% to 80% leukoreduction) allogeneic red cells versus experimental arms of autologous red cells. This partial leukoreduction of the control transfusions minimizes the opportunity for detecting a benefit if allogeneic white cells are important mediators of the effect. In addition, a critical difference may be that the Munich (45,103) study is a single-center study and the Rotterdam study is multicenter (46) with a few dozen patients at each of many centers. Thus far, most single-center trials of leukocyte depletion or autologous transfusion have been successful in demonstrating reductions in morbidity or mortality in allogeneic transfusion recipients, and most multicenter trials have failed to find such benefits. This suggests that the variability introduced by having small numbers of patients treated by varying clinical protocols may have masked any potential benefit. Such procedural variations from center to center have been shown to account for much of the variability in postoperative infection rates in Israel (114). It is relevant that an initial multicenter study by investigators in Leiden failed to find a benefit with leukoreduced transfusions in colorectal cancer surgery, (47) but a later single-center study from the same investigators found a morbidity and mortality benefit to leukodepletion in cardiac surgery (18). Variation in infection control and surgical techniques, such as time of administration of preoperative prophylactic antibiotics importantly affects infection rates, and these variables may compromise studies of transfusion interventions. Nonetheless, it seems clear that allogeneic transfusions, particularly containing white cells, cause an increased risk of postoperative infections, and that this effect can be at least partially abrogated in some settings by leukocyte reduction.

One large randomized trial of universal leukoreduction arrived at the conclusion that leukoreduction neither reduced mortality, morbidity, length of stay, nor hospital costs significantly (115). It did, interestingly, suggest that leukocyte reduction was cost neutral. This study, like all clinical trials, has a number of limitations. First, many patients were included who may not be affected by transfusion immunomodulation. Including outpatients with simple anemia of chronic disease, medical inpatients with modest blood loss, or hypoproliferative anemias may impair the power of a study to detect a true effect in those who are clearly at risk, such as surgical and critical care patients. Second, more than one in eight patients in the leukoreduced arm actually received non-leukoreduced blood. Third, the proportion of patients with protocol violations of this sort was significantly greater in the leukoreduced arm of the study than in the control arm. A likely explanation for this failure of randomization is that when supplies of leukoreduced blood ran short, technical staff switched patients to the non-leukoreduced protocol. Since the transfusion immunomodulation effect is dose-dependent, this could have removed from the leukoreduced arm of the study many of those patients most likely to benefit. Thus while interesting, this study does not address whether leukoreduction reduces morbidity and mortality

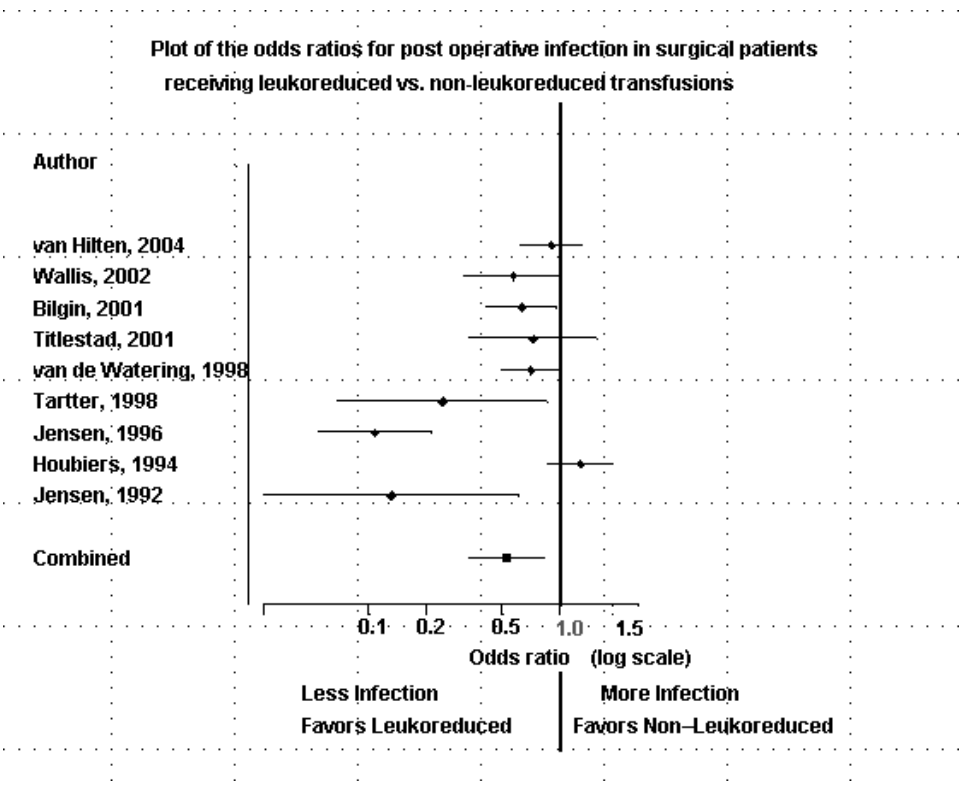

Figure 12.6 The odds ratio for developing postoperative infection in randomized trials of leukoreduced red cells versus that in control recipients of either buffy coat poor, or unmodified whole blood or red cells is shown for the nine published trials in colorectal or cardiac surgery. Results are restricted to patients who actually received transfusions. As can be seen, in eight of nine trials the infection incidence was reduced in the recipients of leukoreduced transfusions, and in six of nine trials this finding was statistically significant in the trial itself. The overall combined result for nine trials, employing a random effects meta-analysis model is a reduction in the odds of postoperative infection in patients receiving leukoreduced transfusions of about 50% ($p = 0.006$). (This figure is based upon work by, and used with permission from, Professor Hongwei Zhao and Hongkun Wang, University of Rochester Department of Biostatistics and Computational Biology, with collaboration from Professor Gary Lyman and Susan Messing. Adapted from Blumberg N, Zhao H, Messing S, et al. Misapplication of the intention to treat principle in clinical trials and meta-analyses of leukoreduced blood transfusions in surgical patients. *Blood.* 2003;102:562a.)

in surgical and other critical care patients, which is where the largest benefits appear to accrue.

Over the last decade a number of meta-analyses have appeared, claiming to demonstrate that transfusion immunomodulation probably does not matter clinically and that leukoreduction is likely of no benefit in reducing postoperative infection (55,116–121). These studies employ seriously flawed methods. One error is failing to calculate a summary odds ratio for the benefits of leukoreduction. The rationale for avoiding calculating a single estimate is statistically significant heterogeneity in the published original studies. Without a summary odds ratio, which is a single number representing the cumulative results of the published clinical trials, a meta-analysis does not exist as such. In addition, statistical heterogeneity is not a good scientific rationale for failing to calculate a summary odds ratio, but rather is an indication for further exploration of the data to investigate possible causes of heterogeneity (122). Even more problematic is that these analyses include nontransfused patients in the individual graphic plots of each study. Nontransfused patients comprise as many as three quarters of the patients in some clinical trials in the published graphs. Nontransfused patients are irrelevant to the questions of whether transfusion immunomodulation has clinically significant effects and whether leukoreduction can reduce such effects. Most seriously, these analyses do not correspond to the actual data from the original studies. Rather for some of the clinical trials, these analyses are imputed outcomes created by the authors of the review (55,116–121). The authors divided in half the number of patients and infections reported in nontransfused patients in several studies. They then added

these infections and nontransfused patients back to the actual data on transfused patients as published. Thus the existing publications that have guided public policy decisions in the United States, when analyzed in detail, have little or no scientific validity.

Summary risk ratios from properly executed recent meta-analyses that restrict their analysis to actual data from transfused patients have demonstrated beyond a reasonable doubt that leukoreduction decreases the odds of postoperative infections in surgical patients by about 50% compared with unmodified red cells or buffy coat poor red cells (113,123).

When the meta-analysis is restricted to studies comparing use of leukoreduced transfusions with control transfusions of partially leukoreduced (about 60% to 80%), buffy coat poor transfusion, a lesser benefit is seen. Compared with buffy coat poor transfusions, leukoreduced transfusions provide a reduction in the odds of postoperative infections of about 37% (Blumberg N, et al, unpublished data, 2004). If the analysis is restricted to studies comparing leukoreduced transfusions with a control arm of leukocyte-replete, unmodified transfusions, the reduction in the odds of postoperative infection is about 57% with leukoreduced transfusions. These figures demonstrate a dose response relationship between the degree of leukocyte reduction, as compared with the control transfusions, and the magnitude of protection from postoperative infections. Greater differentials in extent of leukocyte reduction correspond to a greater relative protection from postoperative infections.

A number of implementation trials of universal leukoreduction have been reported (124–130) These have yielded variable results, as might be expected from before and after studies of infection incidence, length of stay, and other variables heavily influenced by possible changes in case mix, other clinical interventions, and the vagaries of multi-institutional cross-sectional research. Some studies have demonstrated reductions in mortality, morbidity, and/or costs (126–130) and others have not (124,125, 128). None have demonstrated significant increases in morbidity, mortality, or costs with institution of universal leukoreduction, suggesting that at worst, it has been cost neutral and caused no harm, while at best, it has reduced morbidity, mortality, and costs significantly.

These effects are not of minor public health concerns (131). Depending on the percentage of the epidemiologic association that is causal, the number of transfusion immunomodulation associated deaths may be as many as tens of thousands per year, far exceeding those due to other transfusion complications (132). The opportunity to improve care not only involves lives, but dramatic cost reductions. Investigators in Rochester, N.Y., and Aarhus, Denmark, have estimated these savings at $1,000 to $2,000 per allogeneic unit not given (126,133,134). We estimated that the savings to the U.S. health system of universal leukocyte reduction of allogeneic transfusions to surgical patients might be as much as $6 to $12 billion per year, or 1% to 2% of the national health budget (135).

SUMMARY

Transfusions of allogeneic blood to animals or patients are immunomodulatory under many circumstances. Transfused patients are more likely to accept renal allografts. Whole blood recipients have better allograft survival and higher colorectal cancer recurrence rates than similar recipients receiving red cells alone. Allogeneic transfusion recipients are more likely to have postoperative infections than recipients of identical amounts of autologous transfusion. Recipients of leukocyte-depleted transfusions are less likely to develop postoperative infection than recipients of unmodified red cell concentrates. All of these observations can be interpreted consistently by the recent finding that many immune processes, including transfusion, can be characterized in part by their propensity to foster either type 1 or type 2 predominant responses. Allogeneic transfusions lead to decreased type 1 and increased type 2 cytokine secretion in animal models, and medical and surgical patients. Thus a potential unifying theory of transfusion immunology, including the formation of alloantibodies (primarily a type 2 response), allergic reactions (also type 2 in origin) and down regulation of cellular immunity (a type 1 process) has now been proposed for the first time. The single explanation that best fits these clinical and laboratory observations is that allogeneic transfusions mediate clinically significant immunomodulation. Some of these observations have yet to be confirmed in randomized, controlled clinical trials and therefore caution is still warranted in assuming that all these phenomena are cause and effect. Resistance to accepting transfusion effects on cellular immunity and clinical outcomes enveloped the subject of transfusion immunology in a dense fog of confusion and denial during the last 10 years. Continued advances in basic and clinical research will assure that the next 10 years provide better weather.

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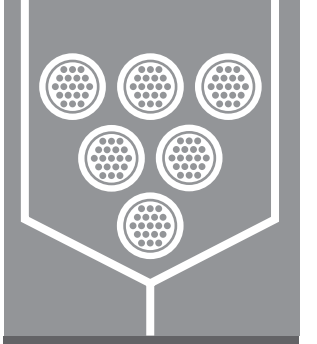

Serious Acute Transfusion Reactions

13

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Blood products are transfused to millions of patients annually in the United States for the purpose of treating bleeding, anemia, thrombocytopenia, clotting factor deficiency, and/or other indications. Thanks to improved screening and testing schemes, donated blood products are unlikely to transmit HIV, HBV, or HCV to transfusion recipients (1). It has been estimated that in the United States the frequency of a repeat blood donor transmitting an HIV, HBV, or HCV infected blood product is in the order of only one in 2.1 × 10e6 units for HIV, one in 2.0 × 10e5 units for Hepatitis B (HBV), and 1 in 1.9 × 10e6 units for (HCV) (2). The risk of transmitting an HTLV-I/II infected donor unit it is in the order of one in 2.9 × 10e6 units (3). While it is true that viruses such as West Nile Virus (WNV) are transmitted by transfusion, steps have been taken to address the risk. It is also true that the possibility of transfusion transmission of new variant Creuztfeldt-Jakob disease (4) raises questions about blood supply safety. However, the risk of transfusion-transmitted viral or prion diseases is currently dwarfed by four potentially fatal adverse reactions that share in common an acute onset during or within a few hours after completing a transfusion. These reactions include acute lung injury, acute hemolysis, sepsis syndrome, and anaphylaxis. This chapter will focus on these four potentially fatal adverse effects of transfusion.

ACUTE LUNG INJURY: TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

Transfusion-related acute lung injury (TRALI) is a subset of acute lung injury (ALI) and is currently the leading cause of transfusion-related mortality (5). To diagnose TRALI there must be a strong temporal relationship between the onset of ALI with a blood product transfusion and no clear temporal relationship with any other known causes of ALI (6,7). The consensus panel report from the April 2004 international symposium in Toronto, Canada, entitled "Towards an understanding of TRALI" (6), stated that a diagnosis of TRALI is established if a patient has no preexisting acute lung injury (ALI) prior to transfusion, and during or within 6 hours after completion of transfusion, there is:

- Acute onset of respiratory distress.
- Hypoxemia characterized by:
  PaO2/FIO2 <300 mm Hg or
  Oxygen saturation (SpO2) <90% on room air or
  Other clinical evidence.
- Bilateral lung infiltrations in the chest radiograph.
- No evidence of left atrial hypertension (i.e., circulatory overload).
- No temporal relationship to an alternative risk factor for ALI.

The above diagnostic criteria are virtually identical to those proposed by a National Heart, Lung & Blood Institute (NHLBI) Working Group on TRALI, when considering patients without other risk factors for ALI (8). Symptoms of TRALI may vary from patient to patient, but often include shortness of breath, difficulty breathing, hypoxia, fever, hypotension, or hypertension followed by hypotension (9). All traditional blood products have been implicated in causing TRALI, including whole blood, RBCs, FFP, platelets (whole blood derived and apheresis), granulocytes, and cryoprecipitate. In addition, TRALI has been associated with allogeneic bone marrow and infusion of IVIg (10–17).

The incidence of TRALI is uncertain, since the condition is probably underdiagnosed, due in part to the lack of a generally applied consensus definition. Until recently most published incidence estimates of TRALI have been based on calculating the number of TRALI cases at a specific institution (using local diagnostic criteria) and then comparing the number of cases to the number of components or patients transfused during a defined study time period. These studies have lead to estimates of one case of TRALI per 5,000 components transfused and one case per 2,400 patients transfused (10,18). It will be interesting to see if these incidence estimates change with the use of a consensus definition.

The pathogenesis of TRALI is incompletely understood and is likely multifactorial. One possible mechanism for TRALI is the interaction between transfused antiwhite blood cell antibodies (such as may be present in FFP or pheresis platelets) with the white blood cells of the transfusion recipient (10,19). A recent study by Kopko et al. (14) showed a correlation between donor antibodies and recipient white cell antigen targets, including monocytes. A second possible mechanism for TRALI is an interaction between antiwhite cell antibodies that are present in a transfusion recipient with white cells that are present in a transfused cellular blood product. A third possible mechanism of TRALI is the infusion of biologically active substances (mediators) that accumulate in cellular blood components (such as RBCs and platelets) during storage (20,21). According to this third mechanism, transfused biologically active mediators (lipids) serve as a *second event* and enhance the NADPH Oxidase of neutrophils that became adherent to the patient's pulmonary capillary endothelium as a result of a physiologic stress, the so-called *first event.* Clinical factors thought to represent first events and predispose a patient to develop TRALI include infection, cytokine administration, recent surgery, and massive transfusion. The adherent NADPH Oxidase enhanced neutrophils then damage the pulmonary capillary endothelium, which causes leakage of protein-rich fluid from the blood into the alveolar spaces (22). This model of TRALI is supported by retrospective data reported by Silliman and colleagues (21). Based on chart reviews, Silliman and colleagues have reported that an association does in fact exist between the presence of a first event or physiologic stress, cellular blood product transfusion, and the development of TRALI. The cellular blood components implicated in these reactions included platelet concentrates, apheresis platelets, and RBCs. They were unable to find an association with patient age or gender, incompatibility of patient–donor blood groups, number of previous transfusions or number and type of previous transfusion reactions. However, they did find that TRALI was associated with a diagnosis of hematologic malignancy ($p < 0.0004$) or cardiac disease ($p < 0.0006$), and with increasing age of platelet concentrates transfused ($p = 0.014$). Pretransfusion and posttransfusion samples from 51 patients who experienced TRALI were analyzed for the accumulation of PMN priming activity. There was significantly more priming activity ($p < 0.05$) in the posttransfusion samples compared to pretransfusion samples and controls.

Regardless of the inciting mechanism, once initiated, TRALI causes major leakage of protein-rich fluid into pulmonary alveolar spaces, which may be manifest in some patients as the production of copious quantities of frothy fluid (with high protein content) from their endotracheal tube, suggesting an exudative process (5,24–28). The chest x-ray in patients with TRALI becomes abnormal at the initiation of the reaction and progresses to a bilateral white out, which is indistinguishable from the pattern seen in ARDS.

Treatment

Fortunately, the great majority of TRALI cases (about 80%) resolve without permanent squeal within 96 hours of transfusion (10), but fatal reactions do occur in about 5% to 10% of cases. Fatalities can occur shortly after the time of onset of the reaction, or may be delayed after a protracted course of mechanical ventilation. Because TRALI occurs infrequently, there are no clinical studies of appropriate treatment after a reaction has occurred, although care often consists of oxygen support with or without mechanical ventilation, and fluid management with avoidance of diuretics. Case reports have suggested worsening of the clinical condition in patients with TRALI following administration of diuretics (15,26). Avoidance of diuretics for patients with TRALI may be justified because the pulmonary edema associated with this condition is noncardiogenic. Patients experiencing TRALI are typically *not* volume overloaded, and, in fact, may be hypovolemic due to the underlying condition or secondary to the extravasations of fluid into the lungs. Therefore, administration of diuretics may lead to hypotension, decreased cardiac output and decreased pulmonary capillary wedge pressure (15,26).

Needless to mention is that volume overload with pulmonary edema is an important differential diagnostic consideration of TRALI. The incidence of circulatory overload is thought to be highest in transfusion recipients who have cardiopulmonary disease or renal failure, or in infants or elderly patients who are anemic but not acutely bleeding. In the event of volume overload with pulmonary edema, treatment includes stopping the transfusion, positioning the patient as upright as possible, administering oxygen, and using a diuretic (e.g., furosemide), if necessary. Severe and persistent symptoms of pulmonary edema should be treated aggressively. In some patients, therapeutic phlebotomy may be necessary.

HEMOLYTIC TRANSFUSION REACTIONS: ACUTE ABO INCOMPATIBLE TRANSFUSION REACTIONS

Hemolytic reactions due to incompatible blood transfusions are currently the second leading cause of transfusion-related mortality, with the majority of these reactions due to transfusion of ABO-incompatible RBCs (5,29,30). ABO hemolytic transfusion reactions are avoidable, and administering the wrong blood product or transfusing the wrong patient causes most cases (31). Signs and symptoms usually occur after the administration of as little as 10 to 15 mL, which is why it is a good practice to closely observe a transfusion recipient during the first 50 mL of an RBC transfusion. In addition, patients who experience a reaction often state that they sense something is wrong, which is why it is a good idea to place a call button within easy reach of a conscious patient, in the event they begin to feel poorly during the transfusion. In the anesthetized patient, the only signs may be unexpected oozing, hemoglobinuria, or hypotension.

Prevention of ABO incompatible transfusions is the best strategy to employ. For an institution to effectively prevent these reactions, it must completely define the local transfusion process and then implement appropriate safe guards. This process consists of several interrelated steps and procedures that represent a complex interplay of activities within the blood bank/transfusion service laboratory, at the patient bedside, and at a variety of interdepartmental interface points between the blood bank and the bedside, including an extreme dependency on numerous diverse human interactions, which are prone to errors (32). Surveillance data point out the failure in patient identification is one of the weakest links in the blood transfusion process, potentially resulting in the erroneous administration of blood to the wrong patient or the administration of the wrong product to an intended recipient and is a key contributing cause to ABO incompatible transfusions (29,33–36). Work by Shulman et al. (36) and others (37) has demonstrated the importance of ongoing audits of the blood transfusion process as a means to identify and reduce errors in the blood transfusion process, although this auditing into compliance strategy does not guarantee that an incompatible transfusion will not occur. Indeed, Shulman has noted that the fewest errors occur in blood component administration practices on those nursing units whose staff routinely performs self-assessment of the blood transfusion process, but that a low level of error is always possible (36). Technology is sorely needed to improve the process of identifying the patient, the patient's pretransfusion sample, the blood product intended for transfusion, and the linkage between these items. However, in the absence of such technology being widely available, a particularly concerted effort must be made to optimize the blood transfusion process, as it currently exists in most hospitals.

Treatment

The transfusion must be stopped immediately (and not restarted), and intravenous fluids must be kept running. The unit should be returned to the blood bank for investigation. ABO-incompatible transfusions frequently result from an identification error that causes two different patients or their pretransfusion samples to be confused with one another. Consequently, whenever a patient or a pretransfusion sample identification error is discovered, a second patient is also potentially at risk. Mainstays of therapy include vigorous treatment of hypotension and maintenance of renal blood flow. Low dose dopamine therapy may be useful to promote renal blood flow. Urinary output monitoring should guide use of fluid therapy to maintain urine flow rates above 1 mL/kg/hr; administration of a diuretic (e.g., furosemide) may be beneficial. A severe hemolytic event may cause systematic activation of coagulation with consumption of clotting factors leading to diffuse coagulopathic bleeding (DIC). Platelets, fresh frozen plasma, and cryoprecipitated antihemophilic factor (cryoprecipitate) may be required. Death occurs in approximately 1 of 30 patients who receive ABO-incompatible RBC. Prevention of a hemolytic transfusion reaction depends primarily on proper identification of the patient, from sample collection through blood administration, and assurance of proper labeling of samples and components.

SEPSIS SYNDROME

Sepsis syndrome following transfusion of bacterially contaminated blood products is currently the third leading cause of transfusion-related mortality, with the majority of these reactions due to transfusion of contaminated platelets (38). Bacteria arising from epidermal or intravascular sources may be introduced into the bag at the time of collection. During storage, bacteria multiply and some may elaborate toxins. Upon transfusion, such units may cause symptoms, even death (39). While sepsis syndrome complicating RBC transfusions is well documented, the per unit risk following platelet transfusions is much greater. Platelets stored at 20 °C to 24 °C are implicated much more frequently than are RBCs (stored at 1 °C to 6 °C) or plasma components (stored below −18 °C). Multiple reports suggest that perhaps in the order of 1:3000 platelet units are bacterially contaminated and that the risk of sepsis syndrome from

platelets is as high as 1:15,000, although this risk may be reduced since March 2004 with the implementation of routine culture of plateletspheresis products by blood collection center (40–50). Johns Hopkins reported a fatality rate of 1:17,000 with pooled whole-blood-derived platelets 1 and 1:61,000 with single-donor apheresis platelets (which were not cultured before use). University Hospitals of Cleveland observed a fatality risk of approximately 1:50,000 per platelet unit.

Patients who are symptomatic with posttransfusion sepsis syndrome can experience high fever, rigors, profound hypotension, and often complain of nausea with or without diarrhea. If a transfusion is suspected to be the cause, it must be stopped and not restarted. The bag, tubing, and other fluids being administered should be returned to the blood bank for immediate investigation to include a Gram stain and culture of remaining component in the bag (and occasionally of the intravenous fluid). Before instituting antimicrobial therapy, it is important to obtain blood cultures from the patient, because finding the same organism in the patient's blood culture as in the blood bag establishes the diagnosis with a high degree of certainty. If the patient is receiving antibiotics at the time of transfusion, blood cultures from the patient may be negative for the organism in question. Because of the high likelihood of fatality, broad spectrum antibiotics should be administered immediately upon suspicion of bacterial contamination. Supportive therapy for other symptoms associated with sepsis should also be undertaken immediately.

ANAPHYLAXIS

Anaphylaxis is a clinical syndrome that represents the most severe systemic allergic reaction, and is a medical emergency that needs prompt attention and if delayed may result in death. Although reaction to blood components are not generally listed as part on the list of inciting agents, an anaphylactic or anaphylactoid reaction during transfusion of a blood component has serious implications for the patient especially if the person continues to have blood replacement needs. An attempt should be made to identify the cause with future blood products selected accordingly.

Incidence

Allergic reactions to blood transfusion have been reported to occur approximately 1% to 3% of all blood transfusions. This estimated rate of allergic transfusion reaction has a range of 1:170,000 to as high as 1:18,000 blood product transfused (51). When component specific risks of allergic reaction are assessed, the incidence of allergic reaction appears to point to platelet preparation as the ones with the highest incidence followed by plasma. Data from 273 consecutive allergic reactions over a 9 year period reported from the Cleveland Clinic, placed the incidence of allergic reaction at 1 in 4,124 components transfused, or 1 in 2,338 transfusion episodes. Severe allergic reactions, those associated with alterations of vital signs, were found in 1 in 30,281 transfusions. When the incidence was calculated for specific products, 1 in 1,070 were for platelet preparation 1 in 2,184 for plasma transfusion and 1 in 3,293 red cell transfused. Of interest, five patients in this report experienced allergic transfusion reactions to autologous red cells complicating our understanding of causal agents responsible for allergic reactions (52). Another report from the Quebec hemovigilance system, estimated allergic and anaphylactic reactions at 1 in 1,598 for platelet preparation and 1 in 23,148 for red cells (53). The most common allergic reaction in hospitalized patients is to ionic radiocontrast dye with estimates as high as 1:450 exposures. Penicillin-derived antibiotics are responsible for the second most common agents with a range of 1:2,500 to 1:6,000 exposures. Severe allergic reactions from this class of antibiotics are responsible for approximately 400 deaths annually (54).

Mechanism of Common Allergic Reactions

Allergic reactions that necessitate medical intervention are thought to divide into anaphylaxis, IgE mediated event, and anaphylactoid reactions that may present similar clinical scenario but are not IgE mediated. A description of four major mechanisms for anaphylaxis to foreign substances is shown in Table 13.1.

In some patients (such as IgA-deficient patients with preexisting anti-IgA antibodies), immediate type hypersensitivity responses may cause rapid death from acute respiratory distress due to laryngeal edema and bronchospasm with hypotension. Like the simple allergic reaction, this

TABLE 13.1

MECHANISMS RESPONSIBLE FOR ANAPHYLACTIC REACTIONS TO FOREIGN SUBSTANCES

1. Classic form of anaphylactic reaction—purely IgE mediated reaction (insect sting and food allergies).
2. Protein—hapten conjugate reaction involving IgE mediation (e.g., penicillin allergy).
3. IgA, IgG mediated compliment activation with anaphylotoxins generation possibly responsible for blood product reaction.
4. Direct activation of mast cells and/or complement activation (ionic contrast media or allergic reaction to platelets).

(Adapted with permission from Bochner BS, Lichtenstein LM, Anaphylaxis. *N Eng J Med.* 1991;324:1785–1790.)

response is due to mast cell degranulation in tissues, including the respiratory tract, skin, gastrointestinal tract, and the cardiovascular system (Table 13.1) (55). If nonrespiratory symptoms predominate, diagnosis may be delayed. Although IgA related reactions could be life-threatening, most allergic reactions are attributed to other mechanisms. A large series of Japanese patients with 4,138 nonhemolytic transfusion reactions, 367 were attributed to immediate onset anaphylactic reactions but haptoglobin deficiency was found to be six times the prevalence of IgA deficiency. Sandler et al. (56) describe findings from sera of patients with history of anaphylactic reactions to blood transfusions. Anti-IgA was detected in 18% of the patients and anti-IgA was detected in 1 of 1,200 random blood donors.

Being the product with the highest rate of allergic reaction, attention must be paid to platelet transfusions. Etiology of allergic reaction associated with platelet products is poorly understood. If the presence of haptoglobin, IgA, and other proteins were responsible for the high rate of anaphylaxis, one would expect plasma products to have the highest incidence and risk for anaphylaxis. Platelets are suspended in plasma containing a significant amount of white blood cells (WBC) and one theory for platelet-derived reaction suggests the impact of leukocyte-derived cytokines. Two Canadian trials have demonstrated no impact in reducing allergic reaction to platelet transfusion with prestorage leukoreduction (57,58). Another mechanism postulates the presence of membrane-derived microparticles on platelet surfaces. Similar to ionic contrast media, activated platelet with membrane derived microparticles are also negatively charged (59,60).

Upon detection and diagnosis of allergic reaction, the transfusion must be stopped and not restarted. The patient should receive appropriate airway management and additional supportive care; epinephrine may be indicated. For IgA-deficient recipients with anti-IgA, subsequent transfusions should be with IgA-deficient components, if possible. For others, plasma reduction of components will minimize the risk of possible recurrence.

Proposed causes for an anaphylactic reaction during a blood transfusion:

1. Antibodies to IgA usually in an IgA-deficient person. Isolated IgA deficiency may affect 1 in 700 to 800 persons of European descent. However, less than 20% of these patients experience an anaphylactic reaction to a blood product.
2. Allergic reactions to other serum proteins or components in the blood product such as platelet derived microparticles.
3. Allergic reactions to drugs or chemicals received by the patient before or during the transfusion.

Diagnosis, Evaluation, and Treatment

Anaphylactic reactions are generalized in nature and have multiple organ system involvement. Symptomatology can range from flushing, hives with or without itching, angioedema with associated stridor, generalized wheezing, shortness of breath, coughing, vomiting, diarrhea, and cardiovascular collapse with shock syndrome (61). Symptoms can occur within minutes of exposure but can also occur within one hour after exposure to the inciting agent(s). Most cases will resolve within hours after initiation of proper treatment, but as many as 20% of cases may have a biphasic course or relapse within hours after treatment (62).

A history of allergic reaction to any medications, biologic materials including blood products and proteins, and food products is an essential part of any complete history. Prior identification of the patient at risk may avoid catastrophic anaphylactic event. Depending on the allergy, premedication may attenuate or avoid an allergic event.

From a practical point, differentiating between anaphylaxis and anaphylactoid reaction is unnecessary since treatment and general management are not different. When an anaphylactic event is suspected, discontinuation of the patient's exposure to the inciting agent is the first step. This is not often possible since multiple suspected agents may already be on board. Shock and vascular collapse must be differentiated from other causes such as sepsis heart failure, hemolytic transfusion reaction, and vasovagal event.

The presence of acute respiratory decomposition must be differentiated from a severe sudden asthma attack, pulmonary embolus, or angioedema. In both vascular and respiratory failure, the presence of skin findings such as flushing, hives, and itching are highly suggestive of anaphylaxis syndrome (63).

Anaphylaxis is a medical emergency and immediate treatment is needed for the patient to survive the episode. Table 13.2 lists the current initial and immediate interventions.

Patients who have experienced transfusion-induced anaphylaxis may benefit from the following diagnostic considerations:

Quantitate the person's pretransfusion serum for IgA level and test for anti-IgA. A person is considered IgA-deficient if serum IgA level is <0.05 mg/dL. Not all patients who are IgA-deficient with anti-IgA will have an anaphylactic reaction on exposure to normal blood components. A person who is not IgA-deficient may have anti-IgA antibodies. This may occur as an autoantibody or due to variation in the person's IgA from normal. Measurement of IgE-type anti-IgA is preferred but may not be available.

If anti-IgA is absent then transfuse unwashed blood components under close medical supervision with adequate

TABLE 13.2
INITIAL PHARMACOLOGIC MANAGEMENT OF ACUTE ANAPHYLAXIS

Drug and Route of Administration	Frequency of Administration	Dose (Adult)	Dose (Child)
Epinephrine 1:1000, IM	Immediately, then every 5–15 min as needed[a]	0.3–0.5 mL	0.01 mL/kg (up to 0.3 mL)
Diphenhydramine, IV, IM or PO	Once patient's condition is stabilized with epinephrine and fluids, then every 4–6 h as needed	23–50 mg	1.25 mg/kg
Ranitidine, IV or PO	Once patient's condition is stabilized with epinephrine and fluids, then every 8 h as needed	50 mg IV or 150 mg PO	1.25 mg/kg IV or 2 mg/kg PO
Steroids: methylprednisolone, IV or prednisone, PO	Once patient's condition is stabilized with epinephrine and fluids, then every 6 h as needed	125 mg IV or 50 mg PO	1 mg/kg IV or 1 mg/kg PO

Note: IM, intramuscularly; IV, intravenously; PO, by mouth.
[a]Until resolution or signs of palpitation, tremor, uncomfortable apprehension, and anxiety occur.

resources to manage a serious anaphylactic reaction. If anti-IgA is absent and the person does not react to unwashed blood components, then evaluate any foods or medications received prior to the transfusion that was associated with the anaphylactic reaction. Pretreatment similar to that of patients with ionic contrast media allergy may be appropriate for those with known reaction to platelet preparation, although no data is available to recommend this approach as a guideline (64).

Managing the patient who has had severe allergic reactions to blood components and who needs a future transfusion.

For the patient who has circulating anti-IgA, the use of IgA-deficient blood components for future transfusion needs is recommended. If the person does not have circulating IgA and has had an anaphylactic reaction to unwashed blood components, then the use of washed blood components for future transfusion needs is recommended.

CONCLUSIONS

Risks of allogeneic blood transfusions have substantially been reduced over the last two decades. Despite these major advances of transfusion medicine, other risks with significant morbidity and mortality still plague the blood supply. Although blood for transfusion can provides significant therapeutic benefits, it is not risk free. Therefore, medical personnel who order, handle, and administer blood components should understand the cause and prevention of these adverse effects. Proper recognition and management of acute adverse effects may be lifesaving for some patients.

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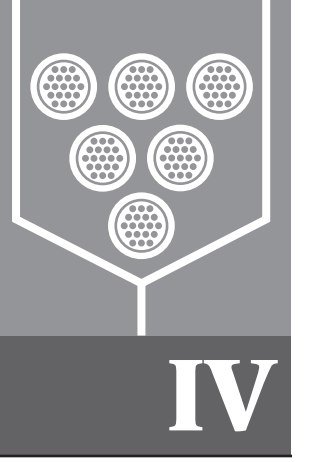
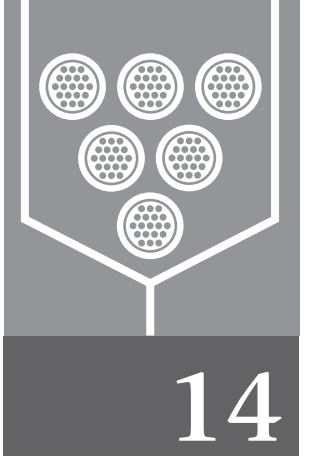


Blood Component Therapy



14

A Surgeon's Guide to Blood Banking and Transfusion Medicine

Kimberly W. Sanford ***Susan D. Roseff***

Over the years, transfusion medicine has evolved to incorporate more than just blood banking services. Dr. Tibor Greenwalt, one of the pioneers of modern transfusion medicine, defines the role of the transfusion medicine specialist to include monitoring "the transfusion practices of their fellow clinicians and advise them on the management of patients needing more sophisticated transfusion service" (1, p. 918). The traditional term *blood banking* has a limited scope that focuses on blood donor screening, blood product collection, component preparation, and blood product release (1). However, the contemporary role of the transfusion medicine physician is to provide medical consultation to clinicians regarding the use of component therapy in a variety of clinical situations, provision of blood for patients with difficult transfusion needs due to the formation of blood multiple antibodies, and to help guide the needs of patients in the face of growing national blood product shortages. Transfusion medicine specialists are also increasingly involved in clinical services such as therapeutic apheresis, stem cell procurement and processing, and advanced laboratory testing for blood compatibility. The medical and technical staff of the transfusion service also serves an educational role, providing information to medical hospital staff, including anesthesiologists and surgeons, as well as nurses, resident physicians, and medical students (2). This chapter describes the basics of blood banking and provides an overview of the functions of the transfusion medicine service. It is important for surgeons and anesthesiologists to realize how these specialists can help in the care of their patients.

REGULATORY AGENCIES AND THEIR IMPACT ON TRANSFUSION MEDICINE

Blood products are considered pharmaceutical agents as well as biologics, by the Food and Drug Administration (FDA). Every aspect of their collection, manufacture, modification, compatibility testing, and distribution is governed by a variety of regulatory agencies as well as quality organizations. Blood manufacturing is required to be performed under strict process control, under current good manufacturing practices (CGMP) to produce a safe, high quality, efficacious product (3). Spurred by the risks of transfusion-transmitted disease and criticism of the way the HIV epidemic was handled by the blood industry, there has been increasing scrutiny and regulatory control of blood banking (4,5). More recently, focus on prevention of errors in medicine has also had an impact on transfusion medicine (6). Due to the lethal effects of transfusing an incorrect unit of blood or acquiring a transfusion-transmitted disease, multiple regulatory agencies now require transfusion medicine services to establish and maintain quality control (QC) and quality assurance (QA) programs for licensing and accreditation. The FDA is directly responsible for promoting the safety of the nation's blood supply and has charged the blood industry with the goal of creating a "*zero risk* blood supply" (7). The Center for Biologics Evaluation and Research (CBER) of the FDA regulates the collection of blood and preparation of components by inspecting blood collection facilities and transfusion medicine services to ensure compliance with the Code of Federal

Regulations (CFR). They also monitor errors and accidents occurring in each facility through a mandatory reporting requirement. CBER works closely with the Public Health Service (PHS) to identify threats to the blood supply, develop standards, and promote an adequate blood supply (8). The FDA has enforcement powers and can levy fines and impose jail sentences on responsible individuals of facilities that are found in violation of regulations. It is imperative for surgical and anesthesia colleagues to realize that the rules and regulations that govern the transfusion service are put in place to ensure patient safety, product efficacy, and to comply with all quality and government mandates.

Voluntary professional accrediting agencies such as the American Association of Blood Banks (AABB) and the College of American Pathologists (CAP) provide voluntary assessment programs for transfusion medicine services and have been established as an industry standard. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) also evaluates transfusion medicine practices in the facilities it inspects, requiring evidence of continuous quality improvement. Most recently the FDA and AABB have incorporated principles from the International Standards Organization (ISO), derived from industry, into their own standards and regulations. Additionally, all clinical laboratories must comply with the quality requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) which have been implemented by the Centers for Medicare and Medicaid Services (CMS), Division of Laboratory Services, under the Department of Health and Human Services (7).

As a result of these requirements, the blood bank is inspected by a variety of agencies on a regular basis. With expectations from the public to provide a zero risk blood supply and additional regulatory requirements, transfusion services are continually revising and improving their own processes to meet their obligations. The flexibility of the transfusion service seen before the appearance of HIV has been supplanted by procedures to maintain consistency (3).

Blood Utilization Review

Each health care facility is required by JCAHO, the AABB, and the Code of Federal Regulations (CFR) to conduct blood utilization review. The CFR requires blood utilization reviews in order for health care facilities to qualify for Medicare reimbursement. Traditionally, most hospitals satisfy this requirement by forming a multidisciplinary committee known as the blood utilization committee (BUC), or transfusion committee, which includes physicians and nurses from many specialties that routinely order blood products. The transfusion medicine director is a member of this committee, but generally does not serve as its chair. The function of the BUC is to assess internally all blood transfusion related processes including blood product orders, transfusion of components, adverse transfusion reactions, product lookbacks, product recalls, and blood shortages. Statistical reports and graphs generated by transfusion medicine are presented to identify trends or patterns in blood usage. Blood waste due to transportation, improper ordering, or handling is also monitored and reviewed by the BUC. The transfusion medicine director will report any sentinel events, such as acute hemolytic transfusion reactions or transfusion-transmitted diseases to the BUC and any other significant events that affect patient care, such as the availability of blood products. The medical staff of the BUC helps create guidelines for blood transfusion and then uses these guidelines to review cases. Transfusion events that are deemed unjustified are discussed with the clinician or their department to reassess current clinical practices. In order to comply with JCAHO, there must be evidence of continuous process improvement and evaluation of individual practitioners (9).

The BUC is typically chaired by a physician who is knowledgeable in transfusion medicine. This individual serves as a resource to other medical staff and as a liaison between practitioners and the transfusion service. They also help create transfusion policies that comply with the regulations affecting the blood industry and provide transfusion education and training of house staff. The BUC routinely and systematically reviews errors or accidents to identify policies or procedures that require modifications or institution of new policies in an effort to improve patient safety (9).

PRETRANSFUSION TESTING

The purpose of pretransfusion testing is to ensure ABO compatibility between the donor and the recipient and to select blood components that will remain viable posttransfusion. Having the correct ABO type is the most important part of compatibility testing. Based on reports to the FDA, the leading cause of death due to transfusion is an ABO hemolytic transfusion reaction (10). These reactions occur due to clerical errors that arise at the time of transfusion (when the patient is not identified correctly), at the time of specimen collection (when the patient is either misidentified or unidentified), or due to blood bank errors during testing. The standards of the AABB require that all blood specimens that will be used for ABO typing and compatibility testing must be labeled at the time of collection, using two unique identifiers to identify the recipient.

Transfusion medicine can only accept specimens that are legibly, accurately, and completely labeled with the patient's name. There must also be a mechanism to identify the person who collected the specimen. At the time of transfusion the transfusionist must positively identify the recipient and verify that all information on the blood component matches the intended recipient (11).

The most important step in pretransfusion testing is to correctly collect and label appropriate specimens from a positively identified patient. Errors in specimen collection can create a devastating chain of events, ultimately leading to an ABO incompatible red blood cell transfusion that can result in a life-threatening hemolytic transfusion reaction (12). One study in New York state estimated that approximately 15% of mistransfusions occurred because a properly labeled unit of blood was administered to a patient other than the intended one, as a result of not following proper identification procedures (13). Another study at Johns Hopkins reported that one in every 71 samples received by transfusion medicine for blood typing, antibody typing, and cross-matching was mislabeled. In addition, one in 2,800 samples was correctly labeled but contained another patients' blood in the sample tube (14).

ABO Typing

When a sample of whole blood is received in the lab, the sample is centrifuged and the red blood cells (RBCs) are separated from the serum or plasma. The supernatant serum or plasma is poured off into another test tube, and the RBCs remain in the original test tube. In this way, the RBCs are tested separately from the serum or plasma. Correctly identifying ABO antigens and antibodies is the most important step to ensure a compatible red blood cell (RBC) and plasma transfusion. Therefore, testing the RBCs and plasma separately is one mechanism to double-check the patient's blood type. A patient's ABO blood type, based on antigens expressed on their red blood cells, leads to the production of predictable, antithetical antibodies (see Table 14.1). ABO antibodies are primarily IgM and capable of causing life-threatening intravascular hemolysis if ABO incompatible blood is transfused. Therefore correctly determining a patient's ABO type is the foundation of all pretransfusion testing (15). Because these antibodies are large, bulky IgM antibodies, agglutination can be easily visualized in a test tube. These naturally occurring antibodies that form without any prior antigenic exposure are reactive over a broad range of temperatures. Their reactivity at room temperature makes their identification simple and rapid. Their reactivity at body temperature makes them clinically significant.

There are three common alleles that may be present at the ABO locus on chromosome 9. A person's ABO blood type is based on the inheritance of genes that encode for glycosyltransferases that add specific sugars to create the A and/or B antigen. Inheritance of an O gene does not generate a functional enzyme. Agglutination tests use manufactured anti-A and anti-B antisera to detect the presence or absence of A or B antigens on a patient's RBCs. Testing to determine which ABO antigens are present on a patient's RBCs is commonly known as forward or cell typing (see Table 14.1) (15).

Conversely, the back type, or serum/plasma type, uses reagent red cells of known ABO type to detect the presence or absence of the reciprocal A or B antibodies. Patients will produce antibodies to antigens they lack. As an example, a type A person will produce anti-B antibodies and type O people will possess both anti-A and anti-B antibodies. Both forward and back typing are required for all patients, except for infants less than 4 months old. Discrepancies between forward and back typing can occur and require clinical correlation with careful serologic testing to determine the patient's correct blood type (15). Though it takes about 15 minutes to perform ABO typing, a discrepancy between the cell and serum type may require a new sample and additional testing, taking anywhere from a few hours to days. If the patient needs blood products, though, group O RBCs can be dispensed while the work-up is in progress.

TABLE 14.1
EXPECTED REACTIONS FOR ABO TYPING

	Patient is Group A	Patient is Group B	Patient is Group O	Patient is Group AB
Anti-A reagent + patient RBC	+	0	0	+
Anti-B reagent + patient RBC	0	+	0	+
A reagent RBC + patient plasma (detects Anti-A)	0	+	+	0
B reagent RBC + patient plasma (detects Anti-B)	+	0	+	0

Rh Typing

Patients are designated as Rh positive or negative to indicate the presence or absence of the D antigen in the Rh system, respectively. The Rh system is composed of more than 40 RBC antigens, however 5 antigens (D, C, E, c, and e) are the most clinically significant for transfusion. Following A and B antigens, D antigen is most important for selecting components for RBC transfusion. However, unlike naturally occurring anti-A or anti-B, anti-D is formed after an Rh negative person is exposed to Rh positive RBCs during transfusion or pregnancy. Anti-D is detected during antibody screening and identification. D is the most immunogenic RBC antigen and immunizing a woman of childbearing potential puts her future pregnancies at risk for hemolytic disease of the fetus/newborn (HDFN) (Table 14.2). Therefore, testing for the presence of D antigen is important in pretransfusion testing (15).

Testing for D antigen involves mixing an aliquot of the patient's RBCs with commercially prepared sera with anti-D. Agglutination of RBCs indicates the presence of D antigen. In the absence of agglutination the patient is designated as Rh negative. With the introduction of more sensitive monoclonal reagents, even patients with a weakened expression of the D antigen will type as Rh positive. This change in sensitivity is evident when older patients who were once tested and designated as Rh negative, test as Rh positive when tested with newer reagents. Some individuals possess a partial D antigen, meaning that they lack part of the D antigen structure. They may type as D negative or D positive, and are at risk of forming anti-D since they become immunized to the portion of the antigen they lack (15). Females of childbearing years who urgently need blood before completion of D testing can be performed should receive Rh negative blood products to prevent formation of anti-D antibodies and prevent HDFN if they become pregnant in the future.

TABLE 14.2
ATYPICAL ANTIBODIES AND REACTIVITY

Antibody	HDFN	HTR
Anti-D	Yes	Yes
Anti-C	Yes	Yes
Anti-E	Yes	Yes
Anti-c	Yes	Yes
Anti-e	Yes	Yes
Anti-M	Occasional	Occasional
Anti-N	Rare	No
Anti-S	Yes	Yes
Anti-s	Yes	Yes
Anti-U	Yes	Yes
Anti-Le^a	No	No
Anti-Le^b	No	No
Anti-Lu^a	No	No
Anti-Lu^b	Mild	Yes
Anti-K	Yes	Yes
Anti-k	Yes	Yes
Anti-Kp^a	Yes	Yes
Anti-Kp^b	Yes	Yes
Anti-Js^a	Yes	Yes
Anti-Js^b	Yes	Yes
Anti-Fy^a	Yes	Yes
Anti-Jk^a	Mild	Yes
Anti-Jk^b	Mild	Yes

Antibody Screen

In addition to ABO typing, pretransfusion testing includes screening the patient's serum or plasma to identify alloantibodies, or antibodies formed after exposure to foreign RBCs. RBC surfaces can contain up to 300 antigens, with their presence or absence determined by genetics. These antigens are capable of immunizing an antigen negative person who becomes exposed either by pregnancy or transfusion. This alloimmunization can stimulate an immune response leading to formation of an alloantibody (16). Atypical RBC antibodies are considered clinically significant when they react at body temperature (37°C) or with antihuman globulin (AHG). AHG is an antihuman IgG antibody that allows bridging of IgG antibodies so agglutination can be seen macroscopically (see Fig. 14.1). Antibodies with these characteristics can be associated with HDFN, hemolytic transfusion reactions (HTR), and decreased donor RBC survival in transfused recipients (see Table 14.2). Therefore, antibody identification and selection of donor units negative for corresponding antigens is an important step for RBC compatibility (see Table 14.3) (15).

A patient's serum is screened for antibodies by adding their serum to a panel of two or three different commercially available donor reagent RBCs. These reagent red blood cells are typed for expression of antigens corresponding to antibodies that are the most common ones implicated in clinically significant delayed hemolytic transfusion reactions. If hemolysis or agglutination occurs this indicates the presence of one or more atypical red blood cell antibodies. The pattern of reactivity in antibody screening is used to identify the alloantibody, but more testing is necessary to confirm the specificity of an atypical red blood cell antibody (15). In the absence of automation, this is a fairly manual process, taking at least one hour. If there are multiple antibodies or rare antibody specificities, it could take many days.

Although there is a risk of becoming alloimmunized with each allogenic transfusion, multiple studies have shown the risk of alloimmunization and subsequent

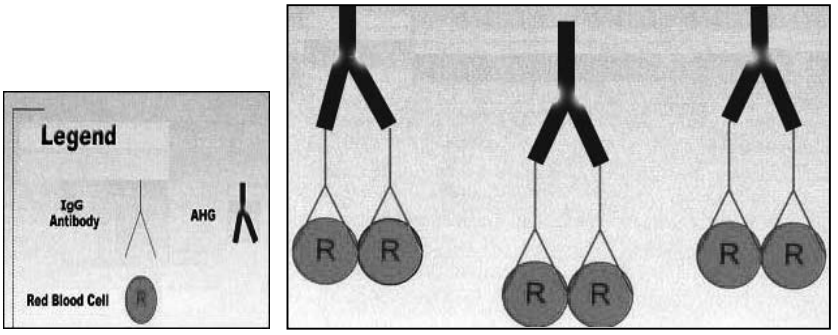


Figure 14.1 Positive direct antiglobulin test (DAT). AHG (antihuman globulin) bridges the bound IgG antibody that is coating RBCs, causing detectable agglutination.

delayed hemolytic transfusion reaction is low. In one study, only 2.6% of patients without detectable alloantibody in pretransfusion testing developed an alloantibody within 7 days of transfusion. In patients who had detectable alloantibodies prior to transfusion, the alloimmunization rate was 8.9%. Despite the development of delayed serologic transfusion reactions in these two groups of patients, only one patient (0.05%) exhibited clinical symptoms of a delayed hemolytic transfusion reaction (17).

Multiple studies of chronically transfused patients, such as patients with hemoglobinopathies, hematologic disorders, or malignancies, also report surprisingly low rates of alloimmunization (18,19). Though one group of investigators found an increasing risk of immunization with subsequent transfusions ranging from 0.45% risk after transfusion with two units to 0.65% after 11 units had been transfused, the overall rate is still low in this population. They also demonstrated that after a patient developed one alloantibody the risk of additional alloantibody formation increased 3.3 times. Despite alloimmunization, there remained a low incidence in the development of delayed hemolytic transfusion reactions in this study (20).

TABLE 14.3
CLINICAL SIGNIFICANCE OF ALLOANTIBODIES

	Antibody
Clinically significant antibodies, requires antigen negative blood and complete crossmatch.	Anti-A, B, D, C, E, c,e, Fya, Fyb, Kell, Jka, Jkb, S, s, U
Benign antibodies without reported hemolytic transfusion reactions.	HTLA, Anti-Xg^a, Bg, Cs^a, Kn^a, JMH, McC^a
Clinically insignificant if nonreactive at 37°C. Unknown significance if reactive at 37°C and required antigen negative blood or crossmatched compatible blood.	Anti-Le^a, Le^b, M, N, P_1, Lu^a, Lu^b, A_1
Antibodies that are sometimes significant and unusual antibodies. Discuss with clinician and transfusion medicine director.	Anti-Vel, Ge, Gy^a, Yk^a, Sd^a, Yt^a, Hy

Antibody Identification

When antibody screening demonstrates the presence of an atypical or alloantibody, antibody identification is the next step. Clinical information, including the patient's clinical diagnosis, pregnancy, and/or transfusion history, and current medications, is helpful in guiding the process. Special procedures may be necessary to identify alloantibodies in patients who have been recently transfused with RBCs (15). A sample can be used for compatibility testing for 3 days. After that time has elapsed, a new sample must be drawn.

The process of alloantibody identification employs the use of an extended panel of 10 different reagent RBCs. The testing can include three phases; immediate spin at room temperature, body temperature, and AHG phases. Some labs choose to eliminate room temperature testing since this can lead to the identification of primarily clinically insignificant antibodies. The pattern of reactivity with panel cells aids in identifying the antibody. If a patient has one or more previously identified alloantibodies, an abbreviated selected panel of regent cells can be done to confirm the alloantibody and exclude additional alloantibodies (15). However, when new antibodies are forming the specificity may be evolving and complete identification is not always possible.

The Presence of Autoantibodies

Occasionally, a patient's serum will contain antibodies that react with their own RBCs, indicating the presence of an autoantibody. Autoantibodies that react only at room temperature are often referred to as cold autoantibodies or cold agglutinins. Cold agglutinins are typically IgM antibodies

with specificity to the I-i antigen or Pr (protease sensitive) antigen on RBC membranes. Cold reacting autoantibodies can form in response to disease states such as Waldenstroms macroglobulinemia, lymphoma, infections with *Mycoplasma pneumonia* or Epstein-Barr virus, medications, or autoimmune disorders such as systemic lupus erythematosus (SLE). However, these antibodies do not usually cause hemolysis and are therefore not clinically significant (15). Again, many labs do not perform room temperature testing and avoid finding these insignificant antibodies. These antibodies can complicate serologic testing, though, and delay the availability of compatible blood. Since these cold reactive autoantibodies are clinically insignificant, if their presence is detected in pretransfusion testing, it is not necessary to use blood warmers when transfusing. Blood warmers are only necessary for clinically significant cold antibodies that are present in cold agglutinin disease or paroxysmal cold hemoglobinuria.

Conversely, warm reacting autoantibodies are capable of causing hemolysis and are usually clinically significant. When these antibodies are present, the direct antiglobulin test (DAT) is positive, showing either IgG, complement, or both are coating RBCs. A DAT, formerly known as the direct Coomb's test, is performed by adding antihuman IgG or antihuman complement to the patient's RBCs. Agglutination is interpreted as a positive result (see Fig. 14.1). The immunoglobulin class of the coating antibody helps classify the autoimmune process and further directs therapy. Note that the DAT can also be positive due to the presence of an alloantibody that has specificity directed toward transfused antigen positive RBCs.

When the DAT is positive this indicates that there are antibodies bound to RBCs. Sometimes, these antibodies are so tightly bound that they are not present in the plasma sample that is used for antibody identification. Therefore, an eluate is performed on the RBC specimen, to release antibodies from antigens on the RBCs. An antibody panel is performed on the eluted serum to determine if the antibody possesses any specificity. Warm autoantibodies are usually directed against high incidence antigens and their specificity is difficult, if not impossible, to establish. These antibodies are generally found in patients with underlying diseases such as malignancy, lymphoproliferative disorders, and autoimmune disorders. (15). The presence of any antibody in a patient's plasma will increase the amount of time necessary to find crossmatched compatible blood. If the patient is unstable, though, they should be transfused with emergency release O or ABO type specific RBCs; transfusion should not be delayed since it may not be possible to obtain crossmatched compatible RBCs (see Fig. 14.2). This will be discussed further later in the chapter.

Review of Previous Record

In addition to performing ABO typing and antibody screening, the patient's previous records should be reviewed. Discrepancies between previous and current ABO and Rh test results may indicate an error in patient identification or sample labeling (15). Review of previously identified atypical antibodies is also important since some alloantibodies may become undetectable over time. In one study, over the course of 1 year, 30% to 35% of alloantibodies became undetectable and over half of the previously identified antibodies became undetectable after 10 years (21). Transfusion with antigen positive cells can cause a delayed hemolytic transfusion reaction, even in the absence of detectable antibody. Therefore, the review of previous records is an important step in the provision of a compatible unit of antigen negative RBCs.

Compatibility Testing

Once the ABO type is complete and the tests for alloantibodies or unexpected antibodies are completed, crossmatching is performed to ensure ABO compatibility and to detect clinically significant alloantibodies, previously undetected on antibody screen. Crossmatching is done by adding a sample of the patient's serum to donor RBCs. Any agglutination or hemolysis indicates that there is an antibody in the patient's serum that is directed against an antigen on donor RBCs. This is an incompatible crossmatch and this unit of RBCs should not be used for transfusion. Samples from patients with negative antibody screens and no previous history of alloantibodies only require an immediate spin crossmatch at room temperature or electronic crossmatch. An immediate spin crossmatch serves as the final check of ABO compatibility. Alternatively, laboratory information systems (LIS) that have been validated and approved by the FDA can be used to perform an electronic crossmatch in lieu of the immediate spin crossmatch. The electronic crossmatch is a clerical check, performed by the computer, to assure that the patient's ABO type is compatible with the ABO type of the unit chosen for transfusion (see Table 14.4). To perform this type of crossmatch, there must be at least two previous samples with concordant ABO results in the computer. Donor unit information including ABO/Rh type and recipient ABO/Rh type is entered in LIS. The donor ABO/Rh type must be confirmed serologically and the LIS must contain logic to prevent release of ABO incompatible units. Electronic crossmatching allows for reduced turnaround time for compatibility testing and reduces unwanted false positives caused by cold agglutinins, which occur with immediate spin crossmatches (16). An electronic crossmatch can only be

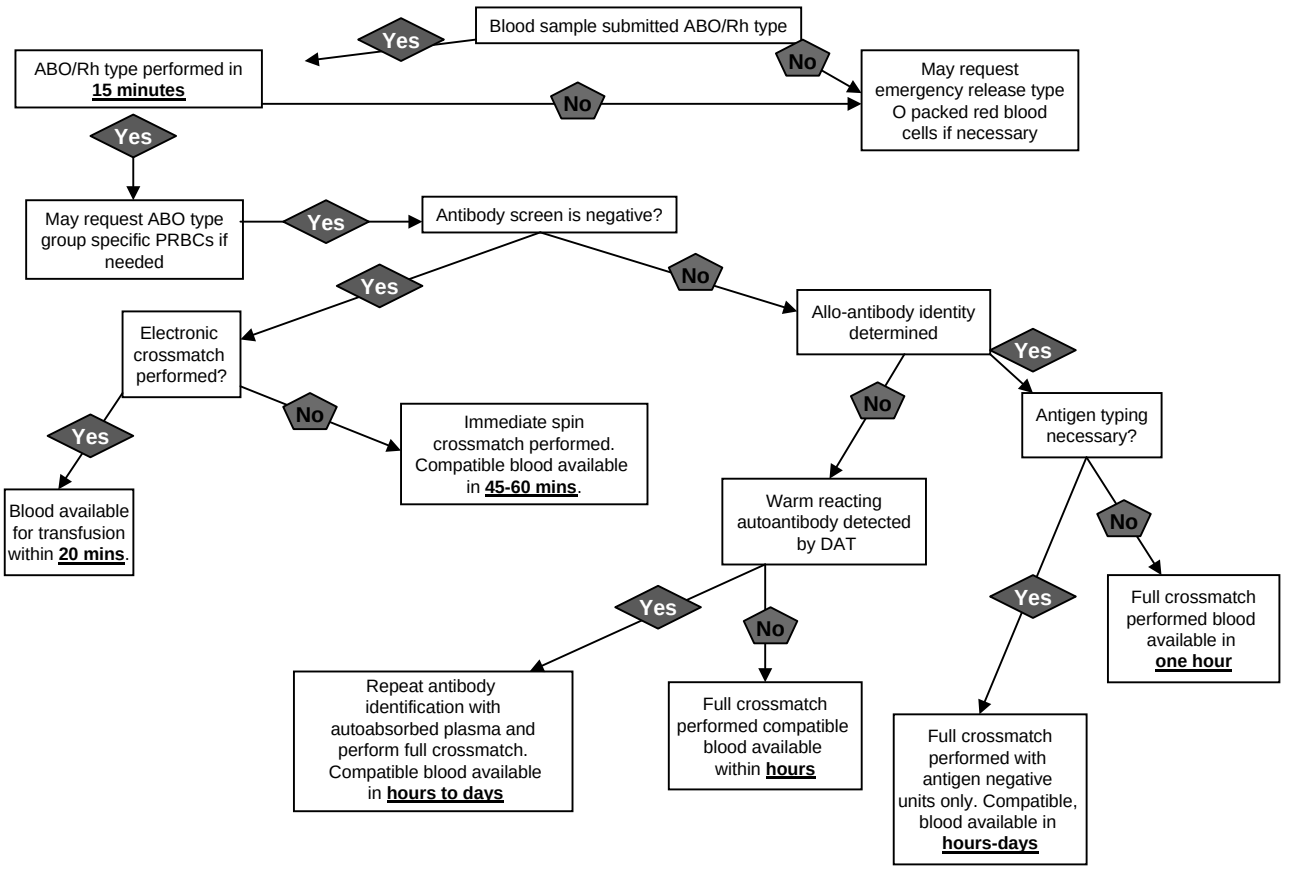


Figure 14.2 Algorithm and time line for obtaining compatible RBCs for transfusion.

performed in the absence of clinically significant alloantibodies in the current sample or any previous samples (see Table 14.3).

For patients with one or more clinically significant atypical RBC antibodies, the clinical significance of each alloantibody must be determined. If an antibody is capable of causing HDFN or a HTR, potential donor RBCs must be screened and only antigen negative units are used. These antigen negative units must undergo a full cross-match, in which patient sera and donor red cells are tested at room

TABLE 14.4
COMPATIBILITIES FOR CELLULAR AND PLASMA PRODUCTS

Patient ABO/Rh Type	RBCs	Platelets	Plasma
O positive	O+, O –	O+, O–, A+, A–, B+, B–, AB+, AB–	O+, O–, A+, A–, B+, B–, AB+, AB–
O negative	O–	O–, A–, B–, AB–*	O+, O–, A+, A–, B+, B–, AB+, AB-
A positive	A+, A–, O+, O–	A+, A–, AB+, AB–	A+, A–, AB+, AB–
A negative	A–, O–	A–, AB-*	A+, A–, AB+, AB–
B positive	B+, B-, O+, O–	B+, B–, AB+, AB–	B+, B–, AB+, AB–
B negative	B–, O–	B–, AB–*	B+, B–, AB+, AB–
AB positive	O+, O–, A+, A–, B+, B–, AB+, AB-	AB+, AB–	AB+, AB–
AB negative	O–, A–, B–, AB–	AB–*	AB–*

*Rh positive may be used in men and postmenopausal women; however, if transfused to women of childbearing potential due to lack of availability of Rh negative products, consider Rh immune globulin to prevent sensitization.

temperature, body temperature, and through the antihuman globulin phase (AHG). Any donor unit demonstrating agglutination or hemolysis with patient serum is designated as an incompatible crossmatch and the unit is inappropriate for transfusion (15). This process is more time-consuming than an electronic or immediate spin crossmatch and can takes a minimum of 1 hour. The algorithm presented in Figure 14.2 illustrates this process and highlights the amount of time each process in the step takes.

Considerations on Requesting Crossmatch Compatible Units

When blood is crossmatched, it is assigned to a specific patient and removed from the general inventory. Crossmatching blood that will not be transfused consumes resources in transfusion medicine and requires a larger blood inventory. This can also increase waste. To prevent this, some hospitals use a maximum surgical blood order schedule (MSBOS) to provide standardization. The MSBOS is a list of surgical procedures with the number of units that will be crossmatched for each procedure. The blood bank can use published guidelines and adapt these by looking at the practices of their surgeons. When a preoperative order for blood exceeds the number indicated on the MSBOS, the order will be clarified to prevent cross-matching units in excess of need. It is recommended that the crossmatch to transfusion ratio (C:T ratio) be 2:1, which still allows for crossmatching twice the number of units for the intended surgical procedure (22). Interestingly, a recent College of American Pathologists (CAP) Q-probe found that the hospitals in their survey that used a using MSBOS actually had more blood wastage than institutions that did not use MSBOS (23). Another proposed algorithm, patient-specific blood ordering system (PSBOS), incorporates patient-specific information such as the patient's weight and hematocrit to determine the patient's average blood volume. Using this information with a surgeon's typical blood loss for a particular surgical procedure, the number of units that need to be cross-matched can be determined (24).

All transfusion services have policies and procedures to prevent unnecessary cross-matching. A hold or type and hold sample is recommended when there is a low likelihood of transfusion. If the patient does need to be transfused, the sample is already in the blood bank and this will expedite typing. A type and screen should be ordered when there is a high likelihood of transfusion.

When there is a planned surgical procedure, and a patient has not been transfused or pregnant in the previous 3 months, nor has any preexisting alloantibodies, many transfusion services allow samples to be collected up to 14 days prior to the procedure. This allows the blood bank to have products ready in advance of the procedure. When patients are known to have many antibodies or have been difficult to crossmatch in the past, this should be communicated to the transfusion service. A sample from the patient should also be sent in advance, but not more than 3 days before need, so there is sufficient lead time to begin a search for compatible blood products.

TRANSFUSION—BASIC GUIDELINES

Prior to transfusion of any blood product, the transfusionist must verify a current physician's order and a current informed transfusion consent (11,15). The component to be transfused and the intended recipient must be positively identified at the bedside. Whenever possible ask the patient to state their name and compare it to the patient's identification bracelet (displaying their name and identification number) to the same information on the intended transfusion component. Confirm ABO/Rh compatibility between the patient and the component by comparing the component tag with ABO/Rh label on the unit. Additionally, the compatibility testing interpretation recorded on the component tag by the laboratory can be reviewed. The expiration date and time of all components should be reviewed and deemed acceptable prior to transfusion. Vital signs must be properly documented. Functional venous access should be established prior to obtaining the unit of blood for transfusion to minimize potential waste of blood products. For cellular components, it is best to use an 18-gauge needle or the largest needle that the venous access can accommodate. To transfuse patients with smaller veins, a 23-gauge catheter can be used but maintain a slower infusion rate to prevent hemolysis of RBCs.

Normal saline should not be added to components to hasten transfusion, since this causes unwanted volume expansion and prolongs transfusion. If a patient is at risk for volume overload, components may be given slowly, however transfusion should not exceed 4 hours per unit. All patients should be monitored for the first 15 minutes of transfusion to observe for reactions, especially an acute hemolytic reaction, anaphylaxis, or a septic transfusion reaction. Transfusion can be started at a rate of approximately 2 mL per minute or faster if hemodynamically tolerated. During massive blood loss, blood may be administered through a large bore catheter as rapidly as tolerated and the vascular access will allow; there is no absolute limit for the speed of transfusion in an exsanguinating patient. After infusion of each transfused component, the volume administered, date and time of completion and patient condition should be documented (15). There should also be a posttransfusion assessment to document the clinical response to transfusion as well as any pertinent

laboratory parameters. It is essential that all practitioners perform these posttransfusion evaluations to assure that the desired clinical endpoint has been achieved.

Any blood component that is not transfused may be returned to the blood bank and reissued to another patient if the container has not been opened or compromised and if it can be confirmed that the component was maintained at the appropriate temperature (11). RBCs cannot remain out of a monitored refrigerator greater than 30 minutes (15). In addition, a unit of RBCs must have at least one sealed segment attached for future compatibility testing. Transfusion medicine must document inspection and acceptability of each unit returned. If these conditions are not met the unit is not suitable to be reissued to another patient and it must be discarded (11), resulting in waste.

Health care professionals including physicians, nurses, and laboratory personnel are responsible for waste of blood products and can have a tremendous impact on reducing its occurrence. Most commonly waste occurs when a unit of thawed or pooled blood products are not transfused (22). Currently, the AABB recommends monitoring waste of blood components due to improper handling. However, there is no published data for acceptable ranges of wastage of blood components. A CAP Q-Probe surveyed multiple institutions in an effort to define a range of acceptable component wastage. The data showed an aggregate rate of waste ranging from 0.6% to 1.0% for RBCs (23). In the face of growing national blood shortages, proper control of blood inventory and prevention of waste is essential.

TRANSFUSION DILEMMAS

Emergency Transfusion and Switching Blood Types

During life-threatening events, there may not be enough time to complete all pretransfusion testing. If blood is needed urgently (before the 15 minutes required for an ABO type and/or the 45 minutes for complete crossmatch), the practitioner should request blood products through the hospital's emergency release procedure. If a patient's ABO blood type is unknown, O RBCs are used. When available, O negative RBCs are administered to females of childbearing potential to prevent possible formation of anti-D, which is capable of causing HDFN in future pregnancies. O positive RBCs should be transfused to males and postmenopausal females if there is not enough D negative inventory, providing the patient does not already have anti-D. The transfusion of D positive blood could result in immunization of the recipient. If possible, collect patient samples for ABO/Rh typing prior to transfusion, so ABO specific blood can be administered. This practice helps conserve O RBCs for patients who need them. Also, testing a sample after transfusion of large amounts of O RBCs will obscure the patient's true blood type.

Emergency situations do not justify exceptions to properly drawn and labeled blood specimens or required procedures identifying the patient during transfusion. In fact, increased attention to patient and sample identification is critical. Due to the chaotic environment surrounding massively bleeding patients, the risk of transfusing a patient with ABO incompatible units of RBCs is potentially great. This is especially true if multiple trauma patients are receiving ABO specific red blood cells instead of group O (25). A physician's signature is required to receive emergency released blood products, however if documentation is not completed during the event it should be complete within 24 hours (15).

Though initially transfusion with group O RBCs may be necessary, ABO/Rh typing of a patient can be performed within minutes. Once the type is known, the patient can receive ABO-specific blood products. For patients with rare blood types, the blood bank may need to switch blood types if ABO-specific products are unavailable. The transfusion medicine physicians will need clinical information regarding expected blood requirements and surgical interventions to assess if a patient will exceed available blood supplies. Decisions to switch ABO or Rh types should be made expeditiously to conserve blood supplies for other patients. Once patients are switched from Rh negative to Rh positive, there is little reason to return to transfusing with Rh negative until the patient stabilizes (15). In historical studies, about 80% of healthy volunteers formed anti-D after exposure to Rh positive red blood cells (26). However a more recent study demonstrated anti-D formation in only 30% of Rh negative patients who had sustained trauma or severely ill patients who received Rh positive RBCs (27). One explanation for this lower immunization rate may be due to stress-induced immune suppression in these patient populations (27). It is also possible that when a patient is bleeding profusely, transfused red blood cells are being lost from the circulation so rapidly that they are not present long enough to stimulate an immune response.

Difficulty Finding Crossmatch Compatible Blood

A difficult situation arises when a patient has multiple alloantibodies, antibodies to antigens found on most RBCs

(high incidence antigens), or autoantibodies. All of these scenarios make it difficult or impossible to find crossmatched compatible blood and can delay transfusion for hours or days. When there are multiple antibodies or antibodies to high incidence antigens, regional blood suppliers and rare donor registries are contacted to help locate antigen negative blood. Sometimes the patients' siblings are a good source of antigen negative products. Cold reactive autoantibodies are clinically insignificant and, if detected, should not delay the provision of compatible RBCs (15).

Patients with warm autoantibodies, with or without autoimmune hemolytic anemia, may also be difficult to transfuse (15). Generally, warm reacting autoantibodies are clinically significant and cause a positive DAT. Since the antibody is usually directed against a common RBC antigen, the patient's serum may be incompatible with all donor units. When this occurs, the transfusion medicine physician will usually talk to the clinician to discuss the difficulty in procuring a compatible donor unit. In this situation it is best to avoid RBC transfusions unless absolutely necessary, and to transfuse the patient only if they exhibit signs and symptoms of anemia, not merely for a falling hemoglobin (16,28). Studies have shown patients producing autoantibodies have an increased risk for allosensitization similar to other multiply transfused patients. Since the autoantibody may mask the presence of a newly formed alloantibody, compatibility testing is further complicated, highlighting the need to transfuse only when there are signs and symptoms of decreased oxygen-carrying capacity (29).

If there is time to plan surgery in advance, the patient should be referred to a hematologist for management of the autoimmune process (28). If transfusion is necessary, extensive testing is usually required. Since the testing requires multiple procedures, it will take a minimum of a few hours, or if it is necessary to send a sample to a reference lab, testing could take days. If crossmatch compatible blood is still unavailable, many blood banks will refer to this as transfusion of ABO compatible blood as *least incompatible* blood. However this term minimizes the effort involved in finding the safest unit for transfusion (30). It is the responsibility of the transfusion medicine physician to explain the antibody identification procedures and compatibility testing to the clinician in this complex setting. Fortunately, RBC transfusion in this setting is unlikely to cause an acute hemolytic transfusion reaction, however the transfused red blood cells will most likely have a shortened survival (30). During transfusion, these patients must be closely observed for signs or symptoms of a hemolytic transfusion reaction, possibly due to an antibody that could not be detected during pretransfusion testing (15).

TRANSFUSION REACTIONS AND THEIR MANAGEMENT

Most transfusions are completed without complications; however, when an adverse reaction occurs the individuals ordering and administering the blood should be trained to handle reactions appropriately. All transfusions should be stopped immediately when a reaction occurs since the severity of some reactions is proportional to the volume of infused blood. There should be documentation of all clinical symptoms and vital signs. The hospital's transfusion reaction policy should be followed. These policies will include procedures for reporting information to the blood bank, returning products/empty bags to the blood bank, and requiring patient samples that must be sent to the blood bank (15). In the surgical setting, transfusion reactions may not be recognized since the patient is unconscious and may have a lower body temperature. In addition, since there are other clinical parameters being impacted during the surgical procedure, changes in vital signs, such as an expected postoperative fever, a transfusion reaction may not be considered in the differential diagnosis. It is essential that changes in vital signs during or soon after transfusion be fully evaluated in accordance with the hospital's transfusion reaction policies.

Acute Hemolytic Transfusion Reactions (AHTRs)

AHTRs are severe and life-threatening transfusion reactions most commonly due to ABO incompatibility between the donor unit and the recipient causing intravascular hemolysis. The person administering the blood products should have ABO incompatibility at the top of their differential diagnosis during an RBC transfusion reaction so that swift action can be taken to avert a patient's death. If a patient has a rise in temperature during RBC transfusion, the person administering the product should recheck the patient's armband and the tag on the unit of blood to ensure that the right unit is being administered. Remember that this is the most common cause of death due to transfusion as reported to the FDA (10).

Typically, the naturally occurring ABO, IgM antibodies are usually responsible for acute life-threatening intravascular hemolysis, not IgG alloantibodies. IgM antibodies are large pentameric molecules capable of spanning intercellular distances between RBCs. Therefore, IgM antibodies cause direct lysis of transfused, incompatible RBCs. Antigen-antibody complexes activate complement, forming a membrane attack complex that creates holes in RBC membranes causing hemoglobin to leak out. One single IgM antibody molecule can activate complement (15).

When ABO incompatible RBCs are administered, there are separate mechanisms in each of the three phases of a hemolytic transfusion reaction. The first phase involves binding of antibody complexes onto the red blood cell membrane creating a systemic inflammatory response causing activation of complement, cytokines, and coagulation factors. The second phase occurs when opsonized red blood cells activate phagocytes and the third phase involves inflammatory mediators, which act on myriad cells causing the manifestations associated with a HTR. As little as 10 to 15 mL of ABO incompatible blood may initiate this systemic response. Initially, patient serum antibodies bind to donor red blood cells (31). Complement activation with formation of membrane attack complexes release hemoglobin from RBCs and anaphylatoxins, such as CD5a and C3a. Hemoglobin release causes hemoglobinemia and hemoglobinuria if the renal capacity for free hemoglobin is exceeded. Released anaphylatoxins react with numerous white blood cells, platelets, smooth muscle, and endothelial cells causing hypotension and bronchospasms, mimicking an allergic transfusion reaction. Antigen–antibody complexes may also activate the Hageman factor (Factor XIIa) and intrinsic coagulation cascade. In this process, bradykinin is generated causing increased capillary permeability, arteriolar dilatation, and decreased systemic arterial pressure. If tissue factor is activated, activation of the extrinsic coagulation cascade occurs resulting in disseminated intravascular coagulation (DIC). DIC results in intravascular formation of thrombi of microvasculature, consumption of coagulation factors, and activation of fibrinolytic system resulting in microvascular bleeding or uncontrolled hemorrhage (15). Hypotension, compensatory vasoconstriction, and deposition of thrombi in renal arterioles impede cortical blood flow contributing to acute renal failure. Free hemoglobin in the kidney does not play an important role in acute renal failure, as was once believed. Due to anaphylatoxin activation and release, proinflammatory cytokines, kinins, and vasoactive amines, shock and death may occur if not promptly recognized and treated (31).

Treatment of AHTR involves prompt treatment of hypotension and restoration of renal blood flow to prevent shock and death. The IV used for the transfusion should be kept open since venous access is difficult if the patient goes into hypovolemic shock. Crystalloid solutions such as normal saline are the first line of support, however, diuretics may be employed to maintain urine output greater than 100mL per hour for the first 24 hours. Pressors may be used to treat shock, however low doses of pressors should be used to improve cardiac output and dilate renal vessels improving renal blood flow, thereby preventing acute tubular necrosis. DIC may be treated with component therapy such as fresh frozen plasma (FFP), cryoprecipitate, and platelets to counteract consumptive coagulopathy and hemorrhage. The use of heparin to dissociate clots formed during DIC is controversial since it may cause further hemorrhage, outweighing its potential benefits (15). In a review of transfusion-related deaths reported to the FDA, the author noted that despite early recognition and aggressive treatment of ABO hemolytic transfusion reactions, the patients usually died by the fourth day following transfusion. However, this data may underestimate the number of patients who survived incompatible blood transfusion since health care facilities were not required to report "near misses," at that time (10).

Sometimes it is difficult to recognize the first signs of a hemolytic transfusion reaction in an unconscious, sedated patient undergoing a surgical procedure. If DIC, hypotension, or any of the signs or symptoms discussed above occurs during surgery when RBCs are being transfused, a transfusion reaction work-up should be initiated. In addition, whenever intraoperative blood samples are grossly hemolytic or the patient's urine turns dark, the possibility of an AHTR should be considered. Again, it is important to have a high degree of suspicion for a transfusion reaction in order to respond promptly. For surgical patients receiving blood products, AHTR and other transfusion reactions should always be a part of the differential diagnosis when investigating hemolysis and DIC.

Delayed Serologic/Hemolytic Transfusion Reactions (DSTR/DHTR)

DSTR and DHTR occur when a patient with an undetected alloantibody is transfused with RBC that expresses the corresponding antigen. DSTRs are usually found incidentally during serologic testing after a recent transfusion. Most antibodies do cause hemolysis, so these reactions are not considered hemolytic. Since some antibodies wax and wane over time, and some may be at undetectable levels during pretransfusion testing, the possibility of a DHTR should be considered in a patient with signs and symptoms of hemolysis after a recent transfusion. As discussed earlier, alloimmunization is uncommon. Even in the face of detectable antibody, clinically significant reactions are rare since two IgG antibodies in close proximity are required to activate complement. Therefore IgG antibodies are less likely to cause intravascular hemolysis (17–20). Additionally, since IgG antibodies are smaller, it is more difficult to span intercellular distances between red blood cells and they are less capable of direct agglutination. Instead, IgG antibodies are more likely to coat red blood cell antigens and are removed extravascularly in the reticuloendothelial system (RES).

DHTRs are usually identified as incidental findings, such as when a patient returns for a postoperative checkup. Any patient who has a drop in hemoglobin and develops jaundice a few weeks after transfusion should be evaluated for a possible DHTR. A DAT should be performed and is usually positive for IgG with the eluate showing specificity for the alloantibody. If the patient is not experiencing any signs or symptoms of anemia, they should be managed conservatively. Since IgG antibodies have an average half-life of 21 days, transfusion usually is unnecessary and the anemia will resolve over the next few weeks as the level of the IgG antibody falls. For patients with rapid hemolysis and symptomatic anemia, transfusion with antigen negative RBC is indicated. Identifying a DHTR will prevent a more time-consuming, unnecessary, and expensive evaluation for the cause of the hemolytic anemia (15).

Septic Transfusion Reactions

Although bacterial contamination of blood components has been overshadowed by concerns over transfusion-transmitted HIV and hepatitis, it is a far more common and serious problem, especially in platelets, stored at room temperature. Due to the recognition of this problem, the AABB implemented a new standard in March 2004 (11). Blood collection facilities and transfusion services are now required to implement processes to prevent the entry of bacterial contaminants into platelets and then prevent the transfusion of platelets that may harbor these pathogens. The blood industry is now implementing procedures to improve skin cleansing techniques and to use special whole blood collection systems that can divert the first portion of the blood collection, known to harbor the skin plug that has the greatest number of bacteria (32). Culture is being performed by some centers while others are using pH and glucose levels to signal the presence of bacterial contamination. All components are inspected prior to release from the blood bank. Red blood cells with gross contamination may have clots or a darker color that can occur as bacteria lyse red blood cells. Platelets may also have a different appearance.

The impact of these changes is not yet known. It is interesting to look at the published reports that lead to these new policies and procedures. One study of 355 transfusion-associated deaths reported to the FDA, found as many as 10% of these were secondary to bacterial contamination of blood products (10). Bacterial growth is more common in platelets since they are stored at room temperature, resulting in better growth conditions for bacterial contaminants. The incidence of bacterial contamination of collected platelets was reported to be as high as one in 1,000 to 2,000 units of platelets (33). In the United States in 1999, there were four million units of platelets transfused. It was estimated that approximately 2,000 to 4,000 bacterially-contaminated platelets were transfused during that time period (34). Though only approximately one sixth to one fourth of these contaminated platelet units would actually cause sepsis (15,35). Gram-positive skin organisms are the most common bacteria cultured from platelets, but death is more commonly associated with gram-negative organisms that elaborate endotoxin.

Contamination with gram-negative organisms is the result of occult, assymptomatic transient donor bacteremia occurring during collection. The growth of the cryophilic bacteria *Yersenia enterocolitica*, *Serratia spp. (liquifaciens* or *marcescens)*, and *Pseudomonas,* is enhanced by the refrigerated storage conditions of RBCs. Endotoxin production by these organisms can also induce fulminant sepsis in the recipient (36). Septic transfusion reactions due to gram-negative rods can be rapidly fatal, with a mortality rate of approximately 60% (33). However, septic transfusion reactions associated with platelets may be largely underrecognized since they can evolve over several hours and present with less severe symptoms. They also have a lower mortality rate (37).

Septic transfusion reactions are characterized by a rise of greater than 2°C or 3°F, severe hypotension or hypertension, DIC, and shock. These classic signs and symptoms may be absent in a surgical patient who is cold or may already have a postoperative fever. When patients experience one of these signs or symptoms during transfusion, the transfusion should be stopped and a sample of blood from the patient be sent for culture. It is imperative to send the remaining component or empty bag to the blood bank for culture as well as reinspection of the unit. Positive culture results from the patient must be compared to the results from the component to link the transfusion reaction to the presence of a bacterial pathogen in the transfused blood. If there is a high degree of clinical suspicion, treatment should be initiated immediately without waiting for the results of cultures. Broad-spectrum antibiotics and appropriate treatment for shock, acute renal failure, and DIC should be initiated immediately (15).

Transfusion-related Acute Lung Injury (TRALI)

TRALI can be a severe life-threatening transfusion reaction characterized by noncardiogenic pulmonary edema temporally related to transfusion. Respiratory symptoms range from dyspnea to acute respiratory distress, usually within 1 to 2 hours after transfusion. Other symptoms include chills, fever (1°F to 2°F), tachycardia, and hypotension or hypertension. All components containing plasma have

been implicated; however, the volume of the component does not determine the severity of the symptoms (38). There is also a report of intravenous immunoglobulin (IVIG) causing TRALI (39). Contrasting this with circulatory overload, central venous pressure and pulmonary wedge pressures remain normal (38). In the largest study to date, TRALI has been reported to cause death in 13% of patients (40) and is the third leading cause of transfusion-related mortality (10). Most patients, though, recover fully if they receive appropriate supportive care that may include intubation.

Several mechanisms for TRALI have been proposed. One mechanism cites passively transfused donor HLA class I or neutrophil antibodies reacting with reciprocal recipient antigens (41). These leukoagglutinating antibodies are most frequently found in multiparous female donors or multiply transfused men (38). Antibody-coated granulocytes in the recipient localize to pulmonary microvasculature, activating complement, and causing a neutrophilic influx which releases damaging enzymes and acidic lipids. These substances damage pulmonary vascular endothelium causing proteinaceous fluid to rush into the pulmonary interstitium. The resultant pulmonary edema is seen as white out on chest x-ray that is unresponsive to diuretics (38). A recent study found that two out of 16 TRALI reactions were the result of antibodies directed against recipient monocyte antigens. This study hypothesizes that multiple different antigen–antibody interactions may cause cellular activation and cytokine release beginning with granulocytes, monocytes, or endothelial cells (42). Two recent studies have implicated donor HLA class II antibodies in TRALI (43,44).

Since not all cases of TRALI seem to involve antigen–antibody interaction, other mechanisms have been sought. One alternative mechanism incriminates biologically active lipids that serve as a neutrophil priming agent in donor plasma. As stored blood ages, NADPH oxidase increases the amount of lipid neutrophil priming agent by as much as 2.1 to 2.8 times (45,46). The neutrophil priming agent also causes endothelial damage of the pulmonary microvasculature and increased vascular permeability leading to pulmonary edema and respiratory distress.

Almost all patients with TRALI require oxygen supplementation with the majority needing mechanical ventilation. When hypotension is severe, pressors may be required. Corticosteroids and diuretics have not been shown to be effective. There is no known way to prevent TRALI since the risk factors for individual patients have not been identified. It is known, though, that donors with HLA or neutrophil specific antibodies can present a risk when their plasma-containing products are transfused. In order to permanently defer implicated donors, it is essential to report suspected cases of TRALI to the blood bank so they can be investigated with the assistance of the collection facility (38).

Febrile Nonhemolytic Transfusion Reactions (FNHTR)

FNHTR are one of the most common transfusion reactions. These reactions are characterized by changes in temperature that may be impossible to distinguish from an AHTR or septic transfusion reaction. AHTR and sepsis should always be considered when a patient has a fever during transfusion, since delay in the diagnosis will increase the risk of death. FNHTR occur at an incidence of approximately 0.5% to 6% during RBC transfusion. With platelet transfusion the incidence has been reported to be as high as 38% (15). Most FNHTR are characterized by a rise ≥1°C or 2°F in temperature, which may be accompanied by chills, rigors, or anxiety unrelated to other medical conditions (47). Inflammatory reactions such as chills, rigors, and hypotension have also been reported in association with transfusion in the absence of fever. Although these reactions are not febrile they are sometimes classified as FNHTR since they share the same pathophysiology (sometimes referred to as FNHTR without fever). Therefore, a rise in temperature is not always a requirement for this type of transfusion reaction (48).

FNHTR are typically benign, though they are uncomfortable and cause anxiety for the patient. There is a higher incidence in multiparous women and in people who are chronically transfused, such as hematology and oncology patients (49). These adverse reactions may occur early in the course of transfusion or could be delayed up to 2 hours after transfusion (50). Since fever could be the harbinger of an acute hemolytic reaction or septic transfusion reaction, the diagnosis of FNHTR is made after excluding more serious etiologies (48).

FNHTR are the result of two different white blood cell mediated mechanisms. The first mechanism is primarily seen with RBCs and is due to recipient antibodies interacting with donor white blood cells. The antigen–antibody complex formed activates complement and the subsequent release of endogenous pyrogens. Also, the direct activity of multiple, biological response modifiers, such as cytokines, plays a role. A second mechanism is related to the persistent production and release of cytokines by white blood cells present in transfused products, which is more frequently seen in platelet transfusion (50). Interestingly, platelets themselves can accumulate cytokines and other biologic response modifiers in the stored component, irrespective of the presence of white blood cells (51). Further studies have shown that despite plasma reduction and washing procedures, CD40 ligand, a potent platelet derived immunoregulator, is still found on the surface of platelets.

This is believed to be the major cause of FNHTR that occur as the result of platelet transfusion in products that have undergone prestorage leukoreduction (52).

As soon as fever is detected, the transfusion should be stopped immediately. Antipyretics, such as acetaminophen, and meperidine, for rigors, are effective. Medications affecting platelet function, such as aspirin, should not be used since they may result in impaired hemostasis. Antihistamines are neither helpful nor indicated for FNHTR. Most febrile transfusion reactions are isolated incidents. For patients who experience repeated FNHTR, leukoreduced components, preferably via prestorage leukoreduction, are indicated. Products that are leukoreduced at the bedside will only be effective if the leukoreduction is done in accordance with the manufacturer's instructions. Leukoreduction can reduce the incidence of FNHTRs, but does not eliminate all reactions (15).

Allergic Transfusion Reactions

Allergic transfusion reactions range from focal urticarial rashes to life-threatening anaphylaxis. These reactions are due to preformed IgE recipient antibodies on mast cells that bind to donor soluble proteins, activating and releasing histamine. Typically, allergic responses escalate with repeated allergen exposure and subsequent transfusion. Anaphylactic reactions can occur in this setting but anaphylactoid reactions can also happen in an IgA-deficient patient who has been previously immunized and possesses IgG or IgM antibodies directed against IgA antibodies. IgA deficiency is considered the most common immunodeficiency in the western population, affecting about 1 in 600 people. Anaphylaxis, though, is still a rare occurrence in IgA deficient patients (53). The most severe anaphylactic reactions are usually found in patients with class-specific IgA deficiency. The only published transfusion death due to anti-IgA occurred in a patient with normal levels of serum IgA and a weak antibody of low specificity (53).

Allergic reactions are classified in a continuum from mild to moderate to severe. Mild allergic reactions are characterized by well circumscribed, localized, erythematous, raised, urticarial lesions or hives, and are not associated with other symptoms. In this setting, the transfusion may be interrupted to administer antihistamines and resumed with if the symptoms resolve. Though the blood bank should be notified, it is not necessary to send blood samples for a transfusion reaction investigation. This is the *only* situation in which restarting a transfusion after an adverse reaction is permitted (54).

Moderate allergic transfusion reactions are more generalized and are characterized by more widespread skin rashes and/or a respiratory component. Severe reactions are usually systemic, causing generalized urticaria, flushing, bronchospasm, dyspnea, stridor, wheezing, gastrointestinal cramps, nausea, vomiting, diarrhea, tachycardia, arrhythmias, and hypotension. Anaphylaxis can also occur. In these reactions, transfusions must be stopped, antihistamines administered, and patient blood samples submitted for transfusion reaction investigation. The patient may also require steroids and pressors (54).

Urticaria may complicate as many as 1% of transfusions (55) with an incidence of anaphylactic reactions estimated at 1 in 50,000 transfusions (56). Anaphylaxis more commonly occurs with platelets and plasma transfusions than with RBCs. Patients with recurrent allergic transfusion reactions should be premedicated with antihistamines a half an hour prior to transfusion. If this is inadequate, 100 mg of hydrocortisone may be indicated. If recurrent moderate to severe allergic transfusion reactions occur despite premedication with antihistamines, transfusion with washed cellular blood products may be indicated. This should be discussed with a physician in transfusion medicine. Known IgA-deficient patients with anti-IgA should be transfused with washed cellular blood products, autologous products, or components obtained from other IgA deficient donors through a rare donor registry (15,53,54).

Circulatory Overload

Although, circulatory overload may receive brief attention, it is one of the most common transfusion reactions. Patients at greatest risk include those with compromised cardiac function, chronic anemia, or those undergoing massive transfusion. The elderly, who develop pulmonary edema due to congestive heart failure, and infants, with their small blood volumes, are also at risk. In some reports, acute pulmonary reactions are identified as the third most common cause of transfusion-related deaths, although this report does not distinguish between TRALI and transfusion-related circulatory overload (10). One study found an incidence of circulatory overload in 1 of 3,168 patients transfused with RBCs (57).

Transfusion-related circulatory overload may present within several hours of transfusion with orthopnea, dyspnea, pedal edema, tachycardia, hypertension, dry cough, headache, chest tightness, cyanosis, and/or rales on auscultation. Circulatory overload occurs as a result of increased central venous pressure due to an increase blood volume from transfused products. There is an accompanying rise in pulmonary blood volume and a decrease in pulmonary compliance with subsequent congestive heart failure and pulmonary edema. Patients with significant anemia are also at increased risk because their heart remains in a hyperkinetic state and may be incapable of tolerating even mild increases of blood volume (58).

If a patient experiences volume overload, discontinue the transfusion, place the patient in a sitting position to improve oxygenation and when necessary, provide supplemental oxygen if the patient is dyspneic. Diuretics should also be administered. To prevent volume overload during transfusion for patients at risk, administer blood products slowly and use diuretics as necessary. Also, start with a smaller volume of a transfused component, such as one unit or red blood cells instead of two (58).

Transfusion-associated Graft Versus Host Disease (TA-GVHD)

TA-GVHD is a life-threatening T lymphocyte mediated immune response with a 90% to 100% mortality rate, with death occurring 1 to 3 weeks after transfusion (59). Despite attempts to use immunosuppressive agents such as cyclosporine, glucocorticoids, antithymocyte globulin (ATG), and anti-T cell monoclonal antibody, patients respond poorly and timing of treatment appears to have no affect on the outcome. In contrast to GVHD following bone marrow transplant, TA-GVHD is almost universally fatal because it targets not only the host or recipient's endothelial lining, but the bone marrow, as well. As a result, TA-GVHD causes bone marrow aplasia and pancytopenia marking the terminal stage of this disease.

Signs and symptoms of TA-GVHD are similar to bone marrow GVHD including skin manifestations, fever, diarrhea, anorexia, nausea, vomiting, and elevated liver function tests (59). The nonspecific symptoms associated with TA-GVHD allow for a broad differential diagnosis. Since patients at risk usually have other underlying comorbidities, this further complicates the recognition of GVHD. Therefore, it is important to have a high degree of suspicion to be able to make the correct diagnosis.

TA-GVHD is more commonly seen in immunodeficient patients who are unable to mount an immune response against transfused donor T lymphocytes. Active donor T cells recognize host histocompatibility locus antigens (HLAs) as foreign, resulting in immunologic reactions against the host (60). The extent of TA-GVHD is determined by the HLA disparity between the donor and the recipient; the greater the HLA disparity the higher the risk that T lymphocytes will mount a response against the host. TA-GVHD can also occur in immunocompetent patients who share an HLA haplotype with a donor. The clinical outcome is the same as an immunosuppressed patient (59).

Currently, irradiation (gamma or x-ray) is the only way to prevent TA-GVHD. Irradiation inactivates T lymphocytes in cellular blood products. All cellular blood products containing viable T cells must be irradiated, including RBC, frozen, deglycerolized RBC, platelet, and granulocyte units (61). AABB standards for blood banks and transfusion services requires irradiation of cellular blood components with a minimum of 2,500 cGy (11). RBC that have been irradiated outdate at 28 days due to accelerated leakage of potassium (59).

SELECTION OF BLOOD COMPONENTS

Transfusion therapy should be initiated after clinical assessment and laboratory assessment are performed. A bleeding patient may have multiple hemostatic abnormalities, therefore, multiple laboratory parameters should be assessed, that may include PT/aPTT; fibrinogen; platelet count; thromboelastogram; etc. If the patient's clinical status allows, all transfusions should be assessed after administration of the blood product and before transfusion of subsequent doses. The risks of transfusion, coupled with the compounding problem of blood shortages makes judicious use of blood products imperative.

Blood products can be collected from either whole blood or via apheresis. Most blood in this country is collected from whole blood donors. The whole blood is collected and transported back to the blood collection facility, where it is separated into components (red blood cells, platelets, and plasma) via centrifugation.

Apheresis/pheresis is a process where a donor is connected to an automated blood processor. Multiple volumes of whole blood are processed by the machine and undergo centrifugation, to separate the different components. In this manner, platelets, plasma, and red blood cells can be collected. Depending on the technology used, these products can be collected to minimize the number of leukocytes, creating a leukoreduced component (62). This is not possible with whole blood collection.

All blood products must be stored at optimal temperature under specified storage conditions to maintain compliance with FDA regulations. This assures their maximal safety and efficacy. All blood banks adhere to these requirements and have policies and procedures that delineate the release and acceptance of blood into the blood bank. Transfusions should be administered so the smallest amount of blood product is administered; in many cases only one unit of RBCs may be necessary to get the desired therapeutic effect. This approach reduces the risks of transfusion and also helps to preserve the blood supply (see Table 14.5).

The decision to transfuse should be made with a careful assessment of risks and benefits. Since each unit of blood transfused carries infectious and immunologic risks, the *minimum* number of units should be used to achieve the desired clinical effect. The specifics of component therapy are discussed elsewhere in the book.

TABLE 14.5
BLOOD COMPONENT CHARACTERISTICS

	Dose	Volume per Dose	Shelf Life	Storage Conditions	Expected Response
PRBC	1 unit	250–325 mL	21–42 days	1°–6°C	1 g/dL increase in Hgb
FFP	Factor replacement: 10–15 mL/Kg	200 mL	Frozen: 1 year; Thawed: 24 hours	Frozen: ≤–18°C Thawed: 1°–10°C	Correct PT/aPTT/INR by replacement of coag factors
Platelets	4–6 pooled whole blood derived platelets or one unit pheresis platelet	200–250 mL	5 days	20°–24°C with continuous and gentle agitation	30–60 X 10^9/L/dose
Cryoprecipitate	10 pooled units	100 mL	Frozen: 1 year Thawed/pooled: 4 hours	Frozen: ≤–18°C Thawed: 1–10°C	Increases fibrinogen, von Willebrand factor, Factor VIII, Factor XIII

SPECIAL PRODUCTS

Autologous and Directed Donations

Patients who are undergoing elective surgical procedures in which transfusion is likely may be candidates for autologous blood donations, such as preoperative deposit or intraoperative and postoperative salvage. The advantages of autologous blood donations include reducing exposure to allogeneic blood, which carries both infectious risk as well as the risk of alloimmunization. In an era of blood shortages, this will also assure the patient that there is blood available. Many patients choose autologous blood because of their fears of transfusion-transmitted infections. Some patients with multiple alloantibodies or those who are IgA-deficient can also help ensure the availability of compatible blood. One can also argue that by using autologous blood, there is more allogeneic blood available for the rest of the population.

In this era of improved blood safety, though, the risks and benefits of autologous donation and transfusion need to be carefully weighed. Autologous donation, though, is not risk-free. It has been found that patients who predeposit their own blood are at risk for preoperative anemia and increase their chances of needing to be transfused (63). In addition, there are clerical errors that result in a patient getting the wrong unit of blood even when autologous blood is available (64). Also, since studies show that 50% or more autologous blood is never transfused, the patient may be put at risk, without any perceived benefit (15). Due to special handling and additional documentation, an autologous unit of blood costs more than an allogeneic unit.

Directed donations are products collected from a specific donor, chosen by the recipient, and intended for only that particular recipient. Typically, these donors are friends or family members of the patient. Most people who request directed products for themselves or their children are concerned about the risks of exposure to transfusion-transmitted diseases, such as hepatitis or human immunodeficiency virus (HIV), and believe blood donated by someone they know will be safer (65,66). The notion that directed blood products are safer than blood from volunteer allogeneic donors has never been proven. There is concern that these products might even be less safe, since many of these donors are first-time donors and older studies show the rate of positive markers for hepatitis are higher than repeat volunteer donors. Since some of these donors feel pressured to donate and are concerned about confidentiality, they may not reveal high-risk behaviors to the collection center (66). Additionally, there is an increased risk for TA-GVHD associated with genetically related donors (59), necessitating that all directed donations must be irradiated prior to transfusion (11).

The use of parents as directed blood donors should also be carefully considered. If the mother has antibodies directed against paternally derived antigens inherited by the baby, it is not safe for the baby to receive components containing plasma from her. Also, if the baby has circulating maternal antibodies, cellular products from the father or his relatives may also be unsafe (65,67,68). Similar to autologous donation, with improved blood safety, the use of directed donors should be carefully considered. As with autologous blood, directed-donor units are more expensive than those collected from volunteer allogeneic donors.

Cytomegalovirus (CMV)—Negative Cellular Blood Products

CMV, a member of the human herpes virus family, is carried in leukocytes and can be transmitted by transfusion.

Though immuncompetent patients can recover from infection, CMV infection in immunocompromised patients may result in a life-threatening illness. Although only 2% of people are actually capable of transmitting CMV, in some populations, up to 70% of the donors may have demonstrable CMV antibodies in their plasma (69). Patients with congenital or acquired immunodeficiency and certain neonates should receive cellular products at reduced risk for transmitting CMV. The AABB considers leukoreduced blood components (containing $<5 \times 10^6$ white blood cells) and products from CMV seronegative donors as reduced risk (15,70,71). Each facility is required to have policies to identify patients at risk for CMV and ensure their provision (11).

Irradiated Blood Products

Irradiated blood products are used to prevent TA-GVHD in immunocompromised patients and immunocompetent patients receiving blood from a related or matched unrelated donor. Although patients with HIV/AIDS are immunocompromised they have not been shown to be at increased risk of TA-GVHD. Likewise, patients undergoing solid organ transplantation are not considered at risk for TA-GVHD. Ionizing radiation (either gamma or x rays) penetrates the nucleus of the lymphocytes and damages the DNA either directly or by generating free radicals or ions that are biologically active. Damaged lymphocytic DNA is unable to proliferate in the host, preventing TA-GVHD (61,72–74). Since irradiated RBC outdate at 28 days due to accelerated leakage of potassium, blood components should be irradiated as close to the time of transfusion as possible (11,74).

Leukocyte-reduced (LR) Blood Products

Transfused white blood cells have been shown to transmit CMV, and other white cell associated viruses, cause febrile non-hemolytic transfusion reactions, and cause alloimmunization that results in refractoriness to platelet transfusion. Leukoreduced blood products, containing $<5 \times 10^6$ leukocytes per unit (11), have been shown to reduce these risks (15,70,71,75–79).

Though still controversial, there is also concern about the immunomodulatory effects of transfused WBCs on the blood recipient. There is data that demonstrates down regulation of cellular immunity after receiving nonleukoreduced blood products. The donor leukocytes modulate the immune system, which in turn has been associated with a decreased rate of rejection of solid organ allografts and spontaneous abortions. Conversely, there is an increased incidence of postsurgical bacterial infections and recurrence of solid tumors during surgical resection if the patient has received allogeneic white blood cells during transfusion. There appears to be a decrease of type 1 cellular immunity. The T cells that are responsible for eradicating microorganisms and preventing tumor recurrence become impaired (80–82).

Leukoreduction is best accomplished prestorage at the blood collection and manufacturing facility, since the process is strictly monitored and controlled. Bedside leukoreduction is another means of leukoreduction, but must be performed according to the manufacturer's specifications to be effective (83).

The need to provide all patients with leukoreduced blood components continues to be controversial. Some hospitals maintain a 100% leukoreduced supply, citing studies showing decreased length of stay and decreased cost of hospitalization (84–86). In a study looking at open heart surgery patients, those who received leukoreduced blood products had a significant reduction in the number of postoperative infections, postoperative length of stay, and the cost of antibiotics. Postoperative infections, reperfusion injury, the rate of febrile nonhemolytic transfusion reactions, and a decrease in inflammatory leukocyte reactions during bypass were also observed (87).

Other institutions provide leukoreduced blood for select patients where they feel there is a proven benefit. Due to the complex nature of large clinical trials, they cite methodological flaws in the data that demonstrate a need for universal leukoreduction. They argue that the cost of universal leukoreduction may not be justified in every patient (88).

Sickle Cell Negative Red Blood Cells

Hemoglobin S can cause irreversible polymerization deforming the biconcave shape of RBCs to a sickle shape in the presence of low oxygen tension. These cells are more likely to hemolyze and do not carry oxygen normally. Patients with homozygous Hgb S have a chronic hemolytic anemia. If a person is heterozygous for Hgb S, they are generally asymptomatic and can serve as a blood donor. Patients with sickle cell disease and neonates are routinely given red blood cells that lack hemoglobin S in order to provide products with the best oxygen carrying capacity (89).

Washed Blood Products

Washed cellular blood products are primarily used to prevent severe allergic reactions to donor soluble proteins after repeated, severe allergic transfusion reactions. Washing blood products reduces their shelf life to 24 hours and can introduce bacteria into the product. Approximately 20% of

red blood cells are lost during washing and approximately 33% of platelets are lost. Washing platelets can also cause their activation, which can affect posttransfusion survival and increments (90). Washed platelets must be infused within 4 hours (11,15). Due to these disadvantages, the need for washed blood products should be carefully weighed and discussed with the transfusion medicine physician. There may also be logistical issues since not all transfusion services wash blood products and the process involves considerable time and cost.

Rh Immune Globulin

Rh immune globulin (RhIG) is a form of concentrated anti-D IgG antibodies derived from pools of plasma from people who possess this antibody. RhIG is available in either an intramuscular (IM) suspension or a suspension, which may be administered either IM or intravenous (IV). The product inhibits the immunization of D (Rh) negative patients who are exposed to D antigen during transfusion or pregnancy. Though a pool of whole blood derived platelets contains only 2 to 3 mL of RBCs and an apheresis unit only about 2 mL, this is enough to immunize a Rh-negative transfusion recipient transfused with Rh-positive platelets. If Rh-negative platelets are not available, an Rh-negative woman of childbearing potential might be transfused with Rh-positive platelets. In these circumstances RhIG should be administered, preferably within 72 hours of transfusion, according to the package insert. One dose of RhIG is capable of preventing immunization for up to 15 ml of Rh-positive red blood cells, contained in 30 units of random donor platelets or seven units of apheresis platelets (15). Using RhIG after massive transfusion is not practical, though, due to the large volume of RBCs transfused. The package insert for WinRho, the IV formulation, only recommends RhIG prophylaxis if the transfused Rh-positive red cell volume is $<$20% of the patient's blood volume. Consultation with the transfusion medicine physician is recommended.

USE OF THERAPEUTIC APHERESIS IN SURGICAL PATIENTS

Apheresis is a process performed with automated cell processors that separate blood into different components using centrifugal force. In plasma exchange or plasmapheresis, the patient's plasma that contains an unwanted antibody or dangerous substance is removed and replaced. The rest of the patient's blood is returned.

Therapeutic apheresis has been performed on patients with acute liver failure awaiting liver transplant. The procedure helps reduce the load of bilirubin and supplies one blood volume of fresh frozen plasma that helps restore hemostasis. There are also case reports where plasma exchange has been used to treat patients with high IgG levels or panel reactive antibodies (PRA) who are about to undergo renal or heart transplant (91). It is believed that reducing the level of PRA either before or after transplant improves the survival of the allograft. Plasma exchange might also be beneficial if there are changes in posttransplant organ function or a biopsy of the graft that demonstrates early histologic changes consistent with rejection (91). There are no large randomized controlled trials at this time.

CONCLUSION: LOOKING AHEAD TO THE FUTURE

Over the next decade there will be continued focus on preventing pathogen transmission through the use of nucleic acid technology as well as the development of pathogen inactivation strategies. With the implementation of bacterial contamination testing, attention will turn more toward the other major causes of death due to transfusion, TRALI and hemolytic transfusion reactions due to ABO incompatibility. The nation's blood supply is not always able to keep up with demand and there will need to be continued efforts at increasing the donor base while evaluating the use of products. As blood donors are more carefully scrutinized and additional processes and procedures are performed on blood products, the cost of blood components continues to rise. Blood safety is not only a matter of what is in a unit of blood, but whether or not the blood is available. Likewise, *transfusion* safety is as important as *blood* safety (12,92).

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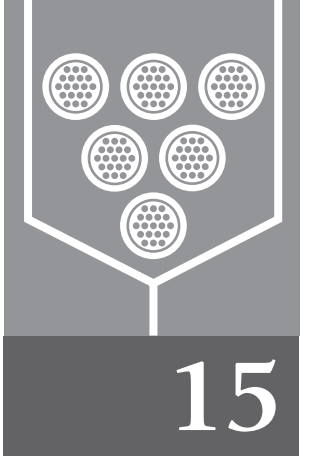

Blood Storage

15

Ian Chin-Yee *Richard K. Spence*

The ability to store blood cells ex vivo for extended periods of time has given rise to the modern blood bank and the specialty of transfusion medicine. In 1914, the introduction of citrate anticoagulant to whole blood revolutionized the practice of blood transfusion by permitting collection and temporary storage of red blood cells. Transfusion no longer had to be done at the bedside through surgically-created connections between donor and recipient. Over the last century, nutrient additive solutions and separation of blood into components has led to the evolution of transfusion from whole blood to more efficient directed component therapy. Testimony to the success of the modern blood bank is the fact that most physicians take for granted a limitless supply of red cell, platelet, and plasma-derived products and give little thought to the consequences of blood transfusion. Our received knowledge that transfusion is life-saving is based historically on the military use of fresh, whole blood, which is a different product from stored red cell concentrates, platelet, and plasma products in current use.

The identification of the risk of transfusion-transmitted diseases such as hepatitis and AIDS has lead to reexamination of many aspects of transfusion practice. Clinical trials in transfusion have lead to the reevaluation of the transfusion threshold and made us aware of the consequences of contaminating leukocytes and storage related changes (1,2). This chapter reviews the changes that occur during ex vivo storage of red blood cells and platelets and the potential clinical consequences of transfusing stored products.

BLOOD PRODUCTS—COMPONENT THERAPY

Red Cell Concentrate

The RBC concentrate is a component of whole blood produced by the removal of plasma and platelet components prior to storage. During the preparation of red cell concentrates, whole blood is collected from the donor in citrate anticoagulant following which RBCs are centrifuged and resuspended in an additive solution that extends cell viability and improves flow rates. Storage media have developed over the years to preserve red cell function and prolong storage times. Typically, 450 mL of whole blood is mixed with 63 mL of anticoagulant/nutritive additive solution, providing an approximate total volume of 510 mL. Currently available anticoagulant-preservative storage media contain either combinations of citrate, phosphate, dextrose, and adenine (CPDA) or CPDA-1 (Table 15.1). Additional additive solutions are commonly added to RBC once plasma/platelets are removed and include combinations of additional dextrose, adenine, sodium phosphate, chloride, citrate, and mannitol (Table 15.2). These additives extend storage time up to 42 days at 1.0°C to 6.0°C depending on the product used. The final red cell concentrate with plasma and platelet rich fractions removed contains approximately 250 mL of volume with a hematocrit in the 55% to 65% range.

Platelet and Plasma Products

The platelet and plasma products are derived from the platelet-rich plasma separated by centrifugation of anticoagulated whole blood. Platelet-rich plasma is fractionated into platelets and plasma by second centrifugation procedure. Unlike RBCs, to maintain hemostatic function platelets are stored at room temperature for up to 5 days. Plasma is generally frozen and stored at –60°C within 6 hours to preserve labile clotting factors. Stored at room temperature, there is progressive loss of the labile coagulation factors; namely, Factors V and VIII. Factor VIII is most unstable and decreases to 50%, 30%, and 6% of baseline values after 1, 5, and 21 days of storage, respectively. Factor V is also labile and decreases to 50% of baseline values after

TABLE 15.1
ANTICOAGULANT PRESERVATIVE SOLUTIONS (MG IN 63 ML)

	CPD	CP2D	CPDA-1
Ratio (mL solution to blood)	1.4:10	1.4:10	1.4:10
FDA-approved shelf life (days)	21	21	35
Content			
Sodium citrate	1660	1660	1660
Citric acid	188	188	188
Dextrose	1610	3220	2010
Monobasic sodium	140	140	140
Phosphate	n/a	n/a	n/a
Adenine	0	0	17.3

storage for 14 days (3). Plasma is also fractionated into albumin, cryopreciptate, specific factor concentrates and gammaglobulin products.

Leukoreduction

White blood cells have previously been considered acceptable contaminants of RBC concentrates and platelet products. Their etiologic role in febrile nonhemolytic transfusion reactions has been known for decades (4) but more recently WBC have also been linked to a number of adverse effects including alloimmunization, transfusion-related graft versus host disease, and immunomodulation (5). In 1998, the Food and Drug Administration recommended universal prestorage leukoreduction (ULR) but no further steps have been taken to make this a regulatory requirement in the United States. Despite the lack of consensus among the transfusion community and additional cost, the majority of blood collection centers have moved to URL. In Canada and Europe, URL was adopted largely to reduce alloimmunization (6) and theoretical transmission of variant Creutzfeld-Jakob disease. Prestorage ULR is preformed by filtration of whole blood or platelet rich plasma following collection and removes >99.9% (3 log reduction) of leukocytes, final leukocyte count less than 5×10^6 (5).

With the exception of fresh-frozen plasma and plasma fractions, the shelf life of blood products is limited. Stored ex vivo under modern blood bank conditions, RBCs and platelets undergo storage-related changes that may alter their efficacy. The effects of storage on RBC and platelet products are discussed below.

TABLE 15.2
CONTENT OF ADDITIVE SOLUTIONS (MG/100 ML)

	AS-1 (Adsol®)	AS-3 (Nutricel®)	AS-5 (Optisol®)
Dextrose	2200	1100	900
Adenine	27	30	30
Monobasic sodium phosphate	0	276	0
Mannitol			
Sodium chloride	750	0	525
Sodium citrate	900	410	877
Citric acid	0	588	0

THE RED CELL STORAGE LESION

Corpuscular Injury

The RBC is a highly evolved cell for the efficient delivery of oxygen to metabolically active tissue. To accomplish this goal, the RBC must maintain several unique properties: (a) deformability, (b) functionally reduced hemoglobin (Fe^{2+}), and (c) 2,3-diphosphoglyerate (2,3-DPG) stores. The RBC has a biconcave disc shape with excess phospholipid bilayer membrane that provides the eight-micron diameter cells sufficient deformability to traverse capillaries of the microcirculation (mean diameter three to eight microns). Maintenance of functionally reduced hemoglobin (Fe^{2+}) and adequate cellular 2,3-DPG allows hemoglobin to bind oxygen at the alveolar/capillary interface in the lungs and unload oxygen in the tissues at low partial pressures of oxygen. Since RBC lack mitochondria and have limited capacity to synthesize nucleotides or proteins, all of these properties are dependent on energy generated by glycolysis.

During ex vivo storage, the metabolic machinery of the RBCs loses function causing a number of morphological and biochemical changes to the RBC that are collectively referred to as the *RBC storage lesion* (Table 15.3) (7). During prolonged storage, ATP is depleted and a predictable sequence of morphologic changes occurs in the RBC, resulting in a loss of its normal biconcave disc shape. Stored RBCs undergo crenation and spicule formation to become echinocytes that subsequently swell to form spheroechinocytes (8). The spicules are eventually shed as lipid vesicles forming spherocytes with a reduced surface to volume ratio. These spherocytic RBCs have an increase in mean cell hemoglobin concentration, increased osmotic fragility, and loss of deformability (9–11). In addition, the loss of endogenous RBC antioxidants results in oxidative

TABLE 15.3
CHANGES IN RED BLOOD CELL DURING STORAGE

Storage Lesion	In Vitro Studies	In Vivo Correlations with Stored RBCs
2,3 DPG depletion	Depletion causes left shift of oxygen–hemoglobin curve.	Restoration of RBC 2,3 DPG occurs within 24–72 hours of transfusion.
ATP depletion	Rapid depletion leads to reversible spheroechinocyte formation.	Poor correlation of ATP levels with 24-hour posttransfusion RBC survival.
Calcium	Increased intracellular levels promote RBC dehydration with echinocytosis and microvesiculation.	None.
Membrane phospholipid loss	Loss of microvesicles correlates with spheroechinocyte formation and increased osmotic fragility.	Decreased vesiculation associated with prolongation of viable storage time and increased survival of AS-1 preserved RBCs.
Protein oxidation	Oxidation of spectrin correlates with RBC membrane vesiculation.	Increased spectrin oxidation seen in congenital spherocytic anemia, but no studies examining relationship with survival of stored RBCs.
Lipid peroxidation	Rate of RBC lipid peroxidation slowed by donors taking antioxidants or addition of antioxidants to stored blood. Addition of antioxidants to stored blood decreases lipid peroxidation, decreases osmotic fragility, and increases RBC deformability.	Decreased lipid peroxidation associated with prolongation of viable storage time and increased survival of AS-1 preserved RBCs.

damage to cytoskeletal proteins (12–14), and membrane phospholipids (15–22). Finally, blood stored for greater than 7 days in acid citrate dextrose is depleted of RBC 2,3-DPG (23) which causes an increase in oxygen affinity (23,24). These combined storage-induced changes in RBCs may functionally limit their ability to travel through fine capillary networks as well as unload oxygen in the peripheral circulation.

Changes in RBC Supernatant Medium

The RBC product is stored in anticoagulant-preservative medium at 1°C to 6°C, which reduces erythrocyte glycolytic activity. Nevertheless, the metabolic activity of RBCs results in the accumulation of lactic acid typically reducing the unit's pH to the 6.7 range. Potassium leaks from red blood cells during storage reaching concentrations as high as 80 mEq per L in one unit of stored blood. Being derived from whole blood, RBC concentrate, is not a *pure* product. It contains other cellular components such as white blood cells. WBCs have a direct effect on RBC integrity, increasing hemolysis and potassium (K^+) leakage (25). Leukoreduction prior to storage improves RBC morphology and decreases hemolysis, microvesiculation, and K^+ leakage (26). It is hypothesized that WBC apoptosis (27) releases toxic oxygen radicals and WBC-associated enzymes cause these adverse effects on RBCs during storage (25,26).

PLATELET STORAGE LESION

Platelets are small anucleate disc-shaped fragments of marrow megakaryocytes that play an essential role in hemostasis. Their normal life span once circulating in blood is estimated at 8 to 10 days (28). Platelets circulate in a nonactivated state. They adhere to injured blood vessels via endothelial surface receptors and through von Willebrand's factor to subendothelial matrix proteins including collagen and fibronectin. Adherence of platelets to subendothelial matrix and exposure to a number of locally generated agonists (collagen, thrombin, ADP epinephrine, thomboxane A_2) leads to changes in platelet shape and aggregation. These steps lead to formation of the platelet plug, which binds fibrinogen and localizes clot formation by immobilizing fibrin formation to its surface.

Platelet concentrates are separated from whole blood by centrifugation after donation. Unlike RBCs, platelets have mitochondria and maintain their metabolic function primarily by aerobic metabolism. Because of this, platelets require storage in gas permeable plastic packs and continuous agitation to ensure adequate gas exchange. At room temperature (20°C), platelet concentrates can be stored for up to 5 days. As with RBCs, collection and storage of platelets results in alteration of the platelet product—changes referred to as the platelet storage lesion (PSL). The PSL is characterized by change in platelet shape from discoid to spherical (29–31), loss of platelet lipid, formation

of platelet microvesicles, (32) and altered expression of membrane glycoprotein receptors GPIb and GPIIbIIIa (33,34). The functional consequences of storage in vivo are uncertain but in vitro testing has demonstrated a reduction in platelet adhesion and aggregation (35–39). The cause of the platelet storage lesion (PSL) is poorly understood and may be related to the type of filtration, storage bag (40), the presence of leucocytes (31,32), or temperature (41). Some researchers have suggested that the platelet storage lesion may be a form of apoptosis (42,43). Many of these storage related changes, including defects in granule secretion, shape changes, and glycoprotein expression, are reversible when platelets are reincubated with fresh plasma and, by implication, following transfusion (44). Platelet effectiveness is usually maintained and posttransfusion platelet recovery generally preserved within the 5 day storage period (44) but the clinical consequences of infusing stored platelets have not been studied extensively. More recently, attention has focused more on the proinflammatory and immunomodulatory effects of platelet products on the host rather than platelet function alone (see below).

Accumulation of Bioactive Substances in Platelet and RBC Products

In addition to accumulation of lactic acid from cell metabolism and leakage of intracellular K^+, a number of bioactive substances accumulate in storage media that can have adverse effects of the transfused host. The metabolic activity of WBC produces cytokines in both RBC (45) and platelet products (46). In the supernatant of platelet concentrates, interleukin 6 (IL-6) (45) is a major cause of nonhemolytic febrile transfusion reactions (47). During RBC storage, increases in cytokines (IL-1, IL-8, and TNF) have been documented (48–52). Cytokine levels are reduced by pre-storage leukoreduction of RBCs, (48–51) which decreases the number of febrile transfusion reactions (49).

Widely varying levels of cytokines have been found in individual units of RBCs (51), and in some units these levels were sufficiently elevated to cause a systemic inflammatory response. In a prospective study of 114 patients undergoing cardiac surgery, Fransen et al. (53) found higher concentrations of bactericidal permeability increasing protein (BPI), IL-6, and markers of neutrophil activation, in transfused versus untransfused patients. Moreover, BPI was found in all units of packed red cells tested at concentrations up to fifteen times preoperative plasma levels in patients whereas IL-6 was undetectable in stored blood. Thus the increase in proinflammatory markers of transfused patients appeared to result directly from infusion of BPI or indirectly by enhancing host release of IL-6. Intraoperative RBC transfusion was also associated with a worse postoperative performance (53). A transfusion related leukocytosis commonly manifest in critically ill patients receiving non-leukoreduced RBC products has also been attributed to high levels of IL-8 in stored blood (54).

Other substances found in storage media include histamine (55), lipids (56), fragments of cellular membrane, and soluble HLA Class I antigens. The soluble lipids share a structural similarity to platelet activating factor (PAF) and are capable of priming and activating neutrophils (56). The source of this lipid is uncertain but it does not appear to originate from WBCs. Several investigators (56–58), confirmed the presence of a non-WBC derived factor which activates neutrophils, in the supernatant of stored RBCs and this increases with the age of the stored products. Silliman et al. (59), demonstrated that both plasma from stored RBCs and the isolated PAF-like lipid caused acute lung injury in isolated rat lungs pretreated with endotoxin. Increased levels of this lipid have also been found in patients after transfusion related acute lung injury (TRALI) reactions and in the blood products associated with TRALI reactions (60).

A number of additional biologically active substances have been identified in platelet concentrates derived directly from platelets themselves or contaminating WBCs (61,62). Level of plasminogen activator inhibitor, vascular endothelial growth factor (61), and RANTES, a proinflammatory chemokine (62) all increase during storage. Clinical consequence of transfusing of infusing these bioactive products in patients is uncertain but RANTES does not appear to account for allergic reactions observed with these products. In animal models, Berman et al. (63) produced pulmonary insufficiency in rats with massive transfusion, implicating an increase in pulmonary capillary permeability from stored platelets as the cause. Removal of platelets and the buffy coat before transfusion eliminated the pulmonary changes. Bisio et al. (64) found extensive accumulations of platelet aggregates in stored platelets and linked these to the development of degenerative changes in the lung capillary endothelial cells, intra-alveolar septae and alveolar epithelial cells in 10 patients following cardiopulmonary bypass and platelet transfusion.

CLINICAL SIGNIFICANCE OF RBC STORAGE LESION

Posttransfusion RBC Viability

The best characterized clinical consequence of the storage lesion is a reduction in posttransfusion RBC viability. For over 50 years, the accepted measure of red cell transfusion efficacy has been 24-hour posttransfusion RBC survival of

greater than 70% (65). This arbitrary value was based on what was practically achievable with preservative solutions at the time. A RBC survival of less than 70% was deemed not to be beneficial in treatment of anemia (65). Twenty-four hour posttransfusion RBC survival was intended as a biologic marker of corpuscular integrity in a manner analogous to increment increases in hemoglobin and not a measure of clinical benefit. Given the functional changes in RBC during storage and the accumulation of bioactive substances in storage medium, 24-hour posttransfusion survival is unlikely to reflect the true clinical effects of transfusion.

Massive Transfusion

Prolonged RBC storage may have important clinical consequences in certain patient populations such as the massively transfused, neonate, renal failure, or critically ill. Massive transfusion is generally defined as replacement approximating or exceeding a patient's blood volume in 24 hours. It can potentially cause several metabolic problems including hyperkalemia, acidosis, citrate toxicity, and reduced tissue oxygen availability due to low RBC 2,3-DPG.

Excess citrate is used to bind calcium in stored blood to ensure its complete anticoagulation and to prevent clotting. CPDA-1 and Adsol red cell concentrates contain 5 mg per mL and 2 mg per mL of citrate, respectively. However, the plasma from Adsol units contains nearly 30 mg per mL of citrate from the CPD anticoagulant used in the initial collection (66). Therefore during massive transfusion, the plasma-containing blood products (FFP, platelets) are the major source of citrate. Citrate is excreted in the urine and metabolized rapidly by the liver in normal patients. The end product of its metabolism is bicarbonate. Citrate infusion causes a transient decrease in ionized calcium. Normal calcium levels are restored by mobilization of skeletal calcium stores. However, in patients who have limited ability to metabolize citrate, particularly those with severe hypotension, hypothermia, hepatic injury, or preexisting hepatic disease, citrate toxicity can cause muscle tremors, increased myocardial irritability, and decreased cardiac output (67). Irreversible ventricular fibrillation may occur at citrate levels of 60 mg per mL.

Hyperkalemia may occur during rapid blood transfusion in patients with severe shock or renal dysfunction, and in patients with extensive muscle necrosis. Some patients may experience a paradoxical hypokalemia resulting from the metabolism of citrate to bicarbonate and increased urinary excretion of potassium (68). In recent years, the ability to infuse large volumes of stored blood rapidly using high-capacity blood warmers has increased the risk of hyperkalemia in critically ill patients (69). Since hyperkalemia and hypokalemia are associated with cardiac dysfunction, close monitoring of potassium levels is recommended in the massively transfused patient. Other populations at risk of hyperkalemia from stored RBCs include neonates where quantity of K+ infused may be disproportionately high for body size.

The ability of red blood cells to bind and release oxygen is dependent on the ability of 2,3-DPG to bind and stabilize deoxyhemoglobin. During red cell storage normal levels of 2,3-DPG are maintained for approximately 10 days then fall rapidly (70). Depletion of RBC 2,3-DPG during storage leads to a left shift in the oxygen-dissociation curve reducing oxygen unloading to ischemic tissue. As result massive transfusion may aggravate existing acidosis caused by hypovolemia Although transfused RBCs regenerate half of their 2,3-DPG levels in 3 to 8 hours after transfusion, complete restoration of 2,3-DPG and normal hemoglobin function occurs may take up to 24 hours (70–72). Recovery of sufficient 2,3-DPG levels to reestablish normal oxygen–hemoglobin dissociation may take 24 to 48 hours, depending on the length of pretransfusion storage and the percentage of circulating red cell mass comprised of transfused erythrocytes (73). This delay in recovery of normal RBC function may be critical in patients with hypovolemic shock. The clinical effect of low 2,3-DPG levels in transfused blood has never been determined but is likely offset by other in vivo variables including increases in cardiac output, vasodilation, and local acidosis (74).

In an animal model of isovolemic hemorrhagic shock model (75), the posttransfusion levels of 2,3-DPG were 50% lower in the stored blood group, but this had no significant limitations on oxygen consumption. Other studies (76–79), found little impairment of work performance, mortality, or ability to withstand hypoxia following exchange transfusion of storage-induced DPG-depleted red cells in man and rats. Valeri et al. (80), found that baboons had no significant effects on cardiac output or VO_2 after transfusion with DPG-depleted blood. Low poststorage 2,3-DPG levels are thus unlikely to have a clinically significant impact on oxygen diffusion.

Critically Ill

In recent years, the deleterious effect of blood transfusion in critically ill population has been extensively studied but it remains unclear whether the adverse effects associated with transfusion are related to prolonged blood storage effect (Table 15.4) (81). A number of retrospective studies (82–86) reported that transfusion was associated with increased morbidity and/or mortality. More importantly, one of the few large randomized controlled trials (1) found unexpectedly, that a restrictive transfusion strategy was

TABLE 15.4
TRANSFUSION OF STORED RBCS AND ASSOCIATIONS WITH MORBIDITY AND MORTALITY

Clinical Outcome	Associations Reported in Clinical Studies	Patient Population	Quality of Evidence
Gastric mucosal pH	Transfusion of RBCs >15 days is associated with a decrease in gastric mucosal pH	Severe sepsis	Prospective, controlled interventional study Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA.* 1993;269(23):3024–3029.
ICU LOS	Transfusion of RBCs >14 days is associated with increased ICU LOS	Medical/surgical ICU	Retrospective Martin CM, Sibbald WJ, Lu X, et al. Age of transfused red blood cells is associated with ICU length of stay. *Clin Invest Med.* 1994;17(suppl 4):B21.
Survival to hospital discharge	Transfusion with RBC >16 days increases mortality	Severe sepsis	Retrospective cohort Purdy FR, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. *Can J Anaesth.* 1997;44(12):1256–1261.
Postinjury MOF	Mean age of blood, number of units >14 days and >21 days independent risk factors for postinjury MOF	Trauma	Prospective cohort Zallen G, Offner PJ, Moore EE, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *Am J Surg.* 1999;178(6):570–572.
Postoperative pneumonia	Risk of pneumonia is increased with mean storage time of RBCs (↑1% per day mean storage time)	Postoperative cardiac surgery	Retrospective cohort Vamvakas EC, Carven JH. Transfusion and postoperative pneumonia in coronary artery bypass graft surgery: effect of the length of storage of transfused red cells. *Transfusion.* 1999;39(7):701–710.
LOS, ICU LOS, mechanical ventilation	No significant associations with length of stay, ICU stay, or mechanical ventilation time with the length of storage	Postoperative cardiac surgery	Retrospective cohort Vamvakas EC, Carven JH. Length of storage of transfused red cells and postoperative morbidity in patients undergoing coronary artery bypass graft surgery. *Transfusion.* 2000;40(1):101–109.
Tissue oxygenation	No change in pCO_2 gap, pH, or any measured oxygenation following transfusion of stored leukodepleted RBCs	ICU	Prospective, double-blind, randomized controlled Walsh TS, McArdle F, MacIver C, et al. Age of stored red cells does not influence indices of oxygenation after transfusion to critically ill patients: randomized controlled trial. *Eur Soc Intensive Care Med.* 2001;27:S247.
Major infection	Transfusion of RBCs >14 days is associated with increased risk of major infection	Trauma	Prospective cohort Offner PJ, Moore EE, Biffl WL, et al. Increased rate of infection associated with transfusion of old blood after severe injury. *Arch Surg.* 2002;137(6):711–716.
Postoperative pneumonia	Duration of storage of the oldest unit is a predictor of pneumonia	Postoperative cardiac surgery	Prospective cohort Leal-Noval SR, Jara-Lopez I, Garcia-Garmendia JL, et al. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. *Anesthesiology.* 2003;98:815–822.

equivalent to and likely superior to the liberal strategy of transfusion. The multicenter trial of Transfusion Requirements in Critical Care (1) randomized 838 critically ill patients to a restrictive (Hb 70–90 g per L) or liberal transfusion strategy (Hb 100 to120 g per L) found the mortality rate during hospitalization was significantly lower (22.2% for restrictive versus 28.1% for liberal strategy, $p = 0.05$. This study not only suggested that restrictive transfusion threshold of 70 g per L was safe but raised the possibility that transfusion of RBC (non-leukoreduced) may be harmful.

Several large observational studies suggest that RBC transfusion in the critically ill may be harmful. A multicenter prospective observational cohort study (87) of 3,534 patients reported that ICU and 28-day hospital mortality was higher in patients receiving blood transfusion versus those who do not ($p < 0.001$) (87). A recent prospective study examining 15,534 trauma patients demonstrated that anemia (hemoglobin <120 g per L) and blood transfusion were predictors of adverse outcome. Most striking, the likelihood of death was almost three times higher in transfused patients after correction for confounding factors such as severity of shock (admission base deficit, lactate, shock index) and anemia (88).

The cumulative evidence from observational studies and randomized controlled studies suggest that blood transfusion may have a deleterious effect on critically ill host independent of illness severity. Prolonged RBC storage duration has been associated with increased mortality, increased length of stay in hospital/ICU, multiorgan system failure, increased infections, and impaired tissue oxygen utilization.

Several studies describe a relationship between storage duration of blood and clinical outcomes such as increased length of stay (LOS) in ICU patients (89), postinjury multiorgan failure (86,90) and mortality (84). Other retrospective cohort studies (91,92), were unable to show an association between the age of stored transfused RBCs with postoperative length of stay in the hospital or ICU, or with the duration of postoperative endotracheal intubation. More recently, these investigators (93) reexamined the CABG population studying the effects of RBC supernatant, platelet supernatant, and plasma components on duration of postoperative ventilation. Their results suggest an association between RBC supernatant volume and prolonged ventilation. These observations support the hypothesis that proinflammatory substances which accumulate during storage of RBC concentrates may impair pulmonary function (53,56,57).

Transfusion-related Immunomodulation (TRIM)

The association of blood transfusion with increased morbidity and mortality in the critically ill may be attributable to increased rates of nosocomial infection. Transfusion of allogeneic blood products exposes the recipient to a wide array of cellular and soluble antigens as well as bioactive substances that may have proinflammatory or immunosuppressive properties. Transfusion-associated immunomodulation (TRIM), first described by Opelz et al. (94), in 1973, was posited to explain the beneficial effect of transfusion on renal allograft survival. This advantage was more recently confirmed in a prospective randomized controlled trial (95). TRIM may also account for the well documented association between transfusions and increased postoperative infection rate (96–99) but patient selection and observational bias in diagnosing infections make it difficult to exclude confounding factors in these studies (96).

Several studies have suggested a relationship between contaminating WBC in the RBC product and transfusion related morbidity and mortality. Two randomized, controlled trials in patients having cardiac surgery showed a significant reduction in 60 day mortality (100,101) and increased infections (101) with transfusion of leukoreduced compared to non-leukoreduced blood. Two large retrospective multicenter studies before and after introduction of prestorage leukoreduction showed only little effect on postoperative infections (87,102) but a reduction in unadjusted mortality rates was observed in one study. A recent meta-analysis of WBC-containing allogeneic blood transfusion and mortality of 14 studies found no association between mortality and blood transfusion across all clinical settings but a subgroup analysis comparing patients undergoing open heart surgery and seven randomized control trials comparing leukoreduced and non-leukoreduced blood showed a significant difference in odds ratio (summary OR for heart surgery 2.26: 95% CI 1.31–3.9, and for non-leukodepleted blood 1.45; 95% CI, 1.0–2.11) (103). The evidence from clinical trials support its benefits for some patient populations such as open heart surgery, but the mechanism may not be necessarily related to TRIM or reduced infection rates.

Transfusion and Oxygenation

The goal of RBC transfusion is to increase oxygen delivery and tissue O_2 utilization. In practice, most clinicians rely on the increased hemoglobin as measure of transfusion success assuming stored transfused cells function as native RBC in oxygen delivery. Several clinical studies have directly examined physiological end-points such as O_2 consumption following transfusion. Although RBC transfusions consistently increase O_2 delivery, only five of 13 studies reported a concomitant increase in O_2 consumption [reviewed in (104)]. In the two studies where O_2 consumption was directly measured calorimetrically, no increase in

O_2 utilization was found despite an apparent increase in calculated O_2 consumption (105,106). In a prospective controlled study, non-leukoreduced blood stored for ≥15 days decreased gastric intramucousal pH in septic patients (105), which is a surrogate marker of splanchnic ischemia (66,107). A more recent double-blind RCT in the ICU did not demonstrate any differences in gastric pHi, or PCO_2 following transfusion of fresh (median 3 days) or old stored leukoreduced RBC's (median 28 days). The differences between these two studies may be secondary to differences in patient populations or the use of non-leukoreduced blood in the earlier trial (105,108) versus leukoreduced RBC product used the more recent study (67). Furthermore, neither transfusion of fresh or old blood showed any beneficial effect of tissue oxygenation as measured by gastric tonometry or global indices of tissue oxygenation. The available evidence is consistent with the conclusion that transfusion of ex vivo stored RBC does not consistently increase tissue O_2 availability, and may result in tissue ischemia.

In animal experiments comparing the effect of fresh (3 day) versus stored (28 day) transfused RBCs on tissue oxygenation in a rat cecal ligation and perforation model of sepsis. Fitzgerald et al. (68) found that rat RBCs stored in CPDA-1 for 28 days did not increase systemic VO_2 (oxygen consumption) as much as fresh transfused RBCs. Van Bommel et al. (69) found that transfusion of rat blood stored for 28 days in saline-adenine-glucose-mannitol (SAGM) but not CPD could improve VO_2 to baseline but did not improve microvascular pO_2 in a hemorrhagic shock model. In vitro comparisons of biochemical and biophysical changes that develop in rat RBCs stored in CPDA-1 for 7 days are similar to human RBCs stored for 28 days (27) indicating that these studies done with 28 day old rat blood likely overestimated the magnitude of human RBCs during storage. Nevertheless, both studies (68,69), highlight the potential limitations of blood stored for extremely prolonged periods by identifying a lack of improvement in VO_2 despite improvement in DO_2. These observations suggest a storage effect that can adversely affect tissue oxygen availability.

Reduced RBC deformability observed during storage may affect diffusion and tissue oxygen availability by impairing microcirculatory hemorheology. In an animal hemorrhagic shock model, Van Bommel et al. (69), found that transfusion of rat RBC stored for 28 days (SAGM or CPDA-1 or CPD) showed significantly reduced deformability compared to fresh RBCs. These cells did not improve microvascular pO_2 which may be secondary to occlusion of the microcirculation by these non deformable cells. Stored RBCs also demonstrate increased aggregation when resuspended in fresh plasma, which can adversely influence microcirculatory rheology by potentially impairing O_2 delivery to tissues (109). These investigators postulate that stored RBCs lose surface sialic acid residues (negatively charged) which thereby increase their aggregability. This happens particularly in the presence of fibrinogen, an acute phase reactant often increased in the critically ill. Storage related loss of deformability or increased aggregation may account for impaired microvascular oxygenation following transfusion reported in preclinical studies (68,69). Using intravital video microscopy, we found that transfusion of stored rat RBCs occlude the rat microvasculature (70). However, it is unclear at this time whether this is secondary to a decrease in deformability causing mechanical obstruction versus erythrocyte adhesion to the vascular endothelium. Several studies have demonstrated that exposure of RBCs and endothelial cells to endotoxin and inflammatory cytokines increased RBC adhesion in vitro using bovine and human endothelial cell monolayers (71,72). Using this in vitro model, we demonstrated that human RBCs stored under standard blood bank conditions adhere to human endothelial cell monolayers under conditions of continuous flow (73). Furthermore, RBC adhesion increases with duration of storage and prestorage leukoreduction eliminates storage-related adhesion. A similar phenomenon was observed in vivo in the rat gastrocnemius muscle where flourescien-labeled stored 7-day-old rat RBCs is more likely to occlude microcirculation than fresh rat erythrocytes (70). Transfusion of adhesive RBCs may further compromise tissue blood flow leading to impaired perfusion and organ dysfunction thus offering an alternate explanation for impaired tissue oxygenation of the critically ill.

In summary, storage of RBCs and platelets ex vivo results in number of changes in the blood product. Unlike wine, blood products do not improve with age. Many of the cellular changes are reversible following transfusion but irreversible changes to RBC and platelets may alter their efficacy. Furthermore, cellular breakdown or activity of contaminating WBC in blood products release a number of biologically active substances that inflammatory or immunomodulatory activity on the transfused host. Accumulating evidence in the critically ill population suggest a relationship between transfusion and storage duration with increased morbidity and mortality. An increase in postoperative infections, length of stay, and postinjury multiorgan failure have all been reported in association with RBC transfusions independent of illness severity and correlation between RBC storage time. The mechanism for these adverse events, and relationship with the RBC storage lesion and/or contaminating white blood cells, remains uncertain and is an area of ongoing study. The logical corollary, to correct the anemia with RBC transfusions, does not consistently improve outcome in clinical trials or tissue oxygenation.

Ideally blood products could be preserved in their native in vivo state and a number of improvements such as nutrient additives and leukoreduction have improved the quality of stored cells. Demanding fresh blood products only is not a sustainable solution to the storage lesion as it would lead to inevitable shortages. In 1991, the Food and Drug Administration considered reducing storage duration to 25 days because of the risk of bacterial contamination with prolonged storage but decided against this policy because of estimated impact on blood supply and observation of Yersinia contamination present in units stored for less than 14 days (74). Thus, the decision is not between fresh or stored blood but between stored or no blood.

The availability of blood products from the modern blood bank is one of the great advances in modern medicine (110). Unfortunately, the success of the modern blood bank has often lead the clinicians to consider stored blood as equivalent to native blood components and a mindset of replacement therapy similar to correction of patients electrolytes was adopted. Transfusion, like all medical interventions, should be used judiciously after careful considerations of risks and benefits. Accepting lower transfusion thresholds is not only safe, but can decrease overall patient exposure to the potentially harmful effects of stored blood products. Despite this evidence, however, a restrictive transfusion policy has still not been universally adopted. The evidence from the TRICC study demonstrated that the restrictive strategy group had a 54% decrease in the total number of units transfused and a trend towards improved overall survival (1).

Alternatives to RBC transfusion also warrant further study. As described elsewhere in this text, erythropoietin has been demonstrated in surgical and critically ill to reduce allogeneic blood exposure (111). Further studies are required to assess whether erythropoietin can improve oxygen delivery and clinical outcomes. Since the response to erythropoietin requires days to weeks and a large proportion of blood transfusions, erythropoietin alone will not eliminate the need for blood in emergent situations.

The challenge remains on how to best maintain the function of this remarkable cell ex vivo for extended periods of time. Our understanding of RBC transfusion require a combination of experimental animal models to evaluate functional properties of the RBC and randomized clinical trials measuring relevant clinical outcomes. The identification transfusion transmitted HIV and hepatitis has lead to intense public scrutiny and demand for a better, safer blood product. Nevertheless, we should keep in mind that blood remains a precious resource and our ability to store and transfuse blood is one of the great advances in modern medicine (110).

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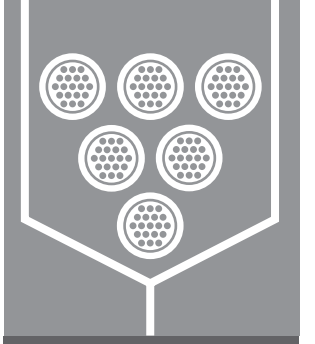

16

Quality Control and Hospital Blood Utilization

Kathleen Walsh-Kaminsky

The concept of quality control in hospital blood utilization is not a new one; this chapter will review emerging quality practices aimed at safeguarding patient care and outcomes in light of growing emphasis on patient safety.

OVERSIGHT

Food and Drug Administration

The Food and Drug Administration (FDA) has federal oversight responsibility for ensuring the safety of our nations blood supply. The Center for Biologics Evaluation and Research (CBER) within the FDA regulates and establishes standards for the collection of blood and blood components used for transfusion and for the manufacture of pharmaceuticals derived from blood and blood components, such as clotting factors. CBER also regulates related products such as cell separation devices, blood collection containers for product preparation, and screening tests that are used to ensure the safety of the blood supply. CBER develops and enforces quality standards, inspects blood establishments, and monitors reports of errors, accidents, and adverse clinical events. CBER works closely with other parts of the Public Health Service (PHS) to identify and respond to potential threats to blood safety, to develop safety and technical standards, to monitor blood supplies, and to help industry promote an adequate supply of blood and blood products. The blood supply now is safer then it ever has been. Practices such as predonation screening have increased the safety of the blood supply, eliminating approximately 90% of unsuitable donors (1).

Through increasing oversight activities, the FDA holds blood establishments to quality standards through monitoring and inspection activities. A substantial role of the FDA in blood safety is to reduce the risk and incidence of infectious agents in the blood supply (1).

American Association of Blood Banks

For over 40 years the American Association of Blood Banks (AABB) has been setting standards for voluntary compliance in blood bank blood component collection, processing, and transfusion. AABB inspections include operational and quality systems evaluation utilizing:

- AABB *Standards for Blood Banks and Transfusion Services.*
- *Code of Federal Regulations.*
- CLIA '88.
- Federal guidance and documents (2).

In addition to blood banks, transfusion services, and blood donor centers, AABB Accreditation Programs include:

Parentage testing: guides laboratories that perform DNA testing to identify and confirm paternity.

Cord blood: accredits cord blood bank facilities which are responsible for collecting, processing, and storing umbilical cord blood stem cells that can be used for transplantation.

Hematopoietic progenitor cells: includes the collection, processing, and transplantation of marrow, peripheral blood, and umbilical cord blood progenitor cells.

Perioperative activities accreditation program: expanded standards program created in 1999, provides a forum

for perfusionists, anesthesiologists, surgeons, and blood bankers who are involved with supervision and maintenance of perioperative autologous transfusion programs.

ISO 9000

The Geneva-based International Organization for Standardization published the ISO 9000 series of standards for quality assurance in 1987 to provide guidelines for consistent quality practices across international borders. ISO is derived from the Greek word *isos*, meaning equal. ISO 9000 aims to establish a level, or equal, playing field of quality assurance from company to company, country to country.

ISO 9000 is primarily concerned with "quality management." This means what the organization does to fulfill:

- The customer's quality requirements, and applicable regulatory requirements, while aiming to
  - —enhance customer satisfaction, and
  - —achieve continual improvement of its performance in pursuit of these objectives (3).
- Increasingly, health care organizations are pursuing utilization of ISO standards in the development of policies and as well as in structuring their quality programs.

UTILIZATION REVIEW PRACTICES

Blood utilization committees are generally responsible for reviewing organizational transfusion activities and practices including: ordering, handling, administration, appropriateness, and reactions. The existing Joint Commission requirement related to transfusion practices is as follows: "The hospital collects data that measure the performance of each of the following potentially high-risk processes, when provided...blood and blood product use" (4).

Individual organizations define the structure, membership, meeting frequency, and criteria utilized in performance measurement. This leads to a lack of uniformity in approach across institutions at the local, state, and national level. This makes for difficulty in benchmarking performance both internally and externally. Often organizations rely on internally developed clinical guidelines for determining appropriateness of transfusion. In addition, organizations must determine based on the scope of services provided, performance improvement priorities and cost considerations areas for review and further study.

As an example, when an organization recognizes and values blood conservation as a standard in patient care, systems must be put in place to allow for the monitoring of this objective. Examples of monitors might include: transfusion rates, morbidity and mortality (with and without transfusion), cost of care including length of stay, transfusions, pharmacology costs, and compliance to drug usage evaluations (usage, indications, and dosing criteria), and changes in practice such as lab testing and quantity sampled.

One of the challenges in performing such analysis in a hospital environment may include: limited resources and lack of easily accessible and accurate data. As an example one may encounter challenges in collecting data in the following situations. Determining transfusion rates versus units transfused, methods of blood conservation utilized in individual cases, bloodless program patients versus transfusion rates, and uniform ICD 9 coding. While analysis includes coding systems, financial systems, and record reviews it may prove beneficial to utilize statistical charges (i.e., no dollars) to allow organizations to more easily obtain variable information it wishes to track.

Increasingly organizations are collecting data related to errors including patient identification. Human factors contribute significantly to errors in hospital transfusion. To reduce the incidence of these errors, hospitals are learning from manufacturing standards that call for standard operating procedures (SOP), adherence to written policy and procedure, and monitoring of processes. Safeguards such as redundant checks in the laboratory and on the patient care unit decrease the likelihood of clerical errors. While no single database exists to analyze the types and causes of errors in transfusion medicine, reviews of mandatory reports of fatalities to the FDA has identified the major causes as clerical errors during the administration of blood and in the laboratory (5).

QUALITY APPROACH

The Institute of Medicine (IOM) defines quality as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes are consistent with current professional knowledge" (6).

Utilizing the six aims for improvement of the IOM is a useful framework for approaching improving the quality of care (6). These six aims are:

1. Safe: avoiding injuries to patients from the care that is intended to help them.
2. Effective: providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit (avoiding underuse and overuse, respectively).
3. Patient-centered: providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions.

4. Timely: reducing waits and sometimes harmful delays for both those who receive and those who give care.
5. Efficient: avoiding waste, in particular waste of equipment, supplies, ideas, and energy.
6. Equitable: providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status.

Components of a successful hospital-based performance improvement program must include planning, measurement, analysis, and documented improvement efforts.

QUALITY CONTROL TOOLS

The utilization of such tools as Root Cause Analysis (RCA) and Healthcare Failure Mode and Effect Analysis (HFMEA) are useful in identifying causes of errors retrospectively and proactively to reduce the potential for errors.

Fundamental Aspects of the HFMEA Process

Adapted from the engineering community by the VA National Center for Patient Safety (NCPS) with assistance from the Tenet Health System (Dallas) "HFMEA uses an interdisciplinary team, process and sub process flow diagramming, failure mode and failure mode cause identification, a hazard scoring matrix, and a decision tree algorithm to identify system vulnerabilities. As part of the process, actions and outcome measures are developed, and management must concur" (7).

The NCPS defines HFMEA as a five-step process that uses a multidisciplinary team to proactively evaluate a health care process. The team uses process flow diagramming, a Hazard Scoring Matrix, and the HFMEA Decision Tree to identify and assess potential vulnerabilities.

Steps included in the HFMEA process include:

Step 1. Define the HFMEA topic.
Step 2. Assemble the team.
Step 3. Graphically describe the process.
Step 4. Conduct a hazard analysis.
Step 5. Actions and outcome measures (7).

Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standard PI 3.20 states "An ongoing, proactive program for identifying and reducing unanticipated adverse events and safety risks to patients is defined and implemented." In the rationale for this standard hospitals should "proactively seek to identify and reduce risks to the safety of patients. Such initiatives have the obvious advantage of *preventing* adverse events rather than simply *reacting* when they occur. This approach also avoids the barriers to understanding created by hindsight bias and the fear of disclosure, embarrassment, blame, and punishment that can happen after an event"(4).

Utilizing tools such as HFMEA allows organizations to analyze in a nonbiased fashion processes such as blood product transfusion. By gaining a greater understanding of the potential failure modes, corrective actions can be implemented prior to an error occurring thereby decreasing the potential for future occurrence.

Organizations must commit the resources to train staff in such methods and allocate resources to allow for sufficient time and energy to adequately complete such an analysis. Encouraging those involved in the process to be active participants in the team adds to the credibility and accuracy of the process.

Root Cause Analysis

Root cause analysis is conducted in response to a sentinel event. A sentinel event is defined as "an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof. Serious injury specifically includes loss of limb or limb function. The phrase 'or the risk thereof' includes any process variation for which a recurrence would carry a significant chance of a serious adverse outcome" (4).

According to the JCAHO an acceptable root cause analysis has the following components:

- The analysis focuses primarily on systems and processes, not on individual performance.
- The analysis progresses from special causes in clinical processes to common causes in organizational processes.
- The analysis repeatedly digs deeper by asking "Why?" then, when answered, "Why?" again; and so on.
- The analysis identifies changes that could be made in systems and processes (either through redesign or development of new systems or processes) which would reduce the risk of such events occurring in the future.
- The analysis is thorough and credible (4).

In August 1999, the JCAHO, issued Sentinel Event Alert #10, entitled *Blood Transfusion Errors: Preventing Future Occurrences* (Table 16.1).

Hemolytic transfusion reaction involving administration of blood or blood products having major blood group incompatibilities is defined by the JCAHO as a sentinel event that requires the conduct of a root cause analysis. In the alert they identified the following risk factors for transfusion errors:

- Variable input (the patients have different blood types).
- Complexity (this includes the technical aspects of crossmatching as well as administering and monitoring the effects of blood).

TABLE 16.1
SENTINEL EVENT ALERT #10—JCAHO

Blood Transfusion Errors: Preventing Future Occurrences

Since the Joint Commission began tracking sentinel events more than 3 years ago, the Accreditation Committee of the Joint Commission's Board of Commissioners has reviewed 12 cases related to transfusion errors. For each of the events reviewed, a root cause analysis was completed.

Ten of the cases resulted in patient deaths while in two of the cases the patients recovered. Also, 11 of the cases were hemolytic reactions, while one was an infectious reaction. Eleven of the transfusion reactions took place in a general hospital with eight occurring in high-risk areas: the operating room, emergency room or intensive care unit, or during resuscitation. One of the 12 cases was in a long-term care organization.

Incomplete patient/blood verifications were identified as at least one of the causes of 8 of the 12 cases. Three of the 12 cases involved the handling or processing of blood samples or blood units for more than one patient at the same time in the same location. In all but one case (contaminated platelets), there were multiple failures to follow established procedures, usually involving the verification of patient identity and correct blood unit for that patient.

The Joint Commission learned of 8 of the 12 cases through self-reporting. Three events were reported by state or federal regulatory agencies, and the Joint Commission learned about one case through media coverage.

Risk Factors

The processes involved in blood transfusion exhibit virtually all of the factors recognized to increase the risk of an adverse outcome:

- Variable input (The patients have different blood types.)
- Complexity (This includes the technical aspects of crossmatching as well as administering and monitoring the effects of blood.)
- Inconsistency (Despite efforts to clearly define procedures within a hospital, there is no standardization across all hospitals.)
- Tight coupling (When steps in a process happen so closely together, if there is a failure in one step there is little opportunity for intervention. It is difficult to interrupt the sequence of the process, especially in an emergency room, operating room or intensive care unit.)
- Human intervention (This is in processes that require a higher level of consistency than is reasonably achievable by health care workers without computer support.)
- Tight time constraints (This occurs especially in an emergency room, operating room or intensive care unit.)

Root Causes Identified

Root causes fell into 7 general areas:

- Patient assessment such as incomplete patient/blood verification.
- Patient assessment such as the signs and symptoms of a transfusion reaction not being recognized.
- Care planning such as no informed consent for a transfusion.
- Laboratory procedures such as multiple samples cross-matched at the same time or a cross-match being started before the order was received.
- Staff-related factors such as insufficient orientation and training or insufficient staffing levels.
- Equipment-related factors such as blood for multiple operating room patients being stored together in the same refrigerator.
- Information-related factors such as incomplete communication among caregivers or patient identification band, specimen label, or blood label errors.

Suggested Strategies for Reducing Risk

The organizations that experienced the sentinel events offered the following risk reduction strategies:

- People-focused actions that included in-service training on transfusion-related procedures and revising the staffing model.
- Process redesign issues such as revising the patient identification band procedures; revising patient/blood verification procedures; revising and implementing new informed consent procedures; discontinuing processing of multiple samples; or discontinuing the use of the room number as the patient identifier.
- Technical system redesign efforts such as enhanced computer support or new patient identification band system.
- Environmental redesign issue such as discontinuing use of an operating room refrigerator for multiple blood units or adding laboratory workstations.

In addition, the Joint Commission suggests the following actions:

- Prohibiting simultaneous cross-matching of multiple patients by the same technologist.
- Not using the patient's room number to identify blood samples or transfusion units.
- Considering the use of "unique" identification bands for patients receiving blood transfusions.
- Introducing a computerized verification step into the process.

(continued)

TABLE 16.1
(continued)

Experts' Recommendations

Experts as well as Joint Commission standards emphasize that health care organizations should have unique patient identifier processes in place. This would be a way to take human fallibility out of the equation, says Kathleen Sazama, MD, JD, a professor of pathology and laboratory medicine at MCP Hahnemann University in Philadelphia.

Sazama says organizations should use a handheld bar code reader to read both bar coded wristbands on every patient and a bar code identifier on the tag of the components. If the bar code reader fails to confirm the identity between the wristband and the tag, then the health care worker cannot proceed with the transfusion.

James B. Battles, PhD, a professor of medical education for the University of Texas Southwestern Medical Center, Dallas, says bar coding can help but he believes there still is not a good patient identification system in place. He says a major effort needs to be made to study the problem and find the best method.

(Reprinted with permission from JCAHO: Sentinel Event Alert #10, August 1999).

- Inconsistency (Despite efforts to clearly define procedures within a hospital, there is no standardization across all hospitals.)
- Tight coupling (When steps in a process happen so closely together, if there is a failure in one step there is little opportunity for intervention. It is difficult to interrupt the sequence of the process, especially in an emergency room, operating room, or intensive care unit.)
- Human intervention (This is in processes that require a higher level of consistency than is reasonably achievable by health care workers without computer support.)
- Tight time constraints (This occurs especially in an emergency room, operating room, or intensive care unit.)

Root causes identified fell into six general categories:

- Patient assessment such as incomplete patient/blood verification.
- Patient assessment such as the signs and symptoms of a transfusion reaction not being recognized.
- Care planning such as no informed consent for a transfusion.
- Laboratory procedures such as multiple samples cross-matched at the same time or a cross-match being started before the order was received.
- Staff-related factors such as insufficient orientation and training or insufficient staffing levels.
- Equipment-related factors such as blood for multiple operating room patients being stored together in the same refrigerator.
- Information-related factors such as incomplete communication among caregivers or patient identification band, specimen label, or blood label errors (8).

CAUSES OF ERRORS

Most people do not deliberately make errors. Errors are most often caused by systems and process failures and may be described as "the consequence of poor design or operation of an overall 'system' in which people play active roles" (5). Human factors also play a role in errors.

Orientation and Training

Cited by the JCAHO as the most frequently occurring root cause in transfusion errors (8), orientation and training is an area that organizations should evaluate in a proactive manner to help reduce the potential for errors.

Patient Identification

In a study of transfusion errors in New York state based on 10 years of data, the authors identified that 56% of errors involved a single error in a patient care area with the most frequent reported type of "event being the administration of properly labeled blood to a patient other than the one for whom it was intended" (9). In root cause analysis of sentinel events reported to the JCAHO related to transfusion, greater than 65% determined patient identification to be a root cause (8). Clerical and systems issues also are associated with errors including mislabeled specimens, mislabeled products, ordering for wrong patient, and improper storage.

Many organizations have put in place policies to encourage redundant checks to ensure a reduced potential for patient identification errors. These practices may include: laboratory quality control processes, two-person identification of blood product-recipient information at point of release from laboratory and two-person verification of blood type, product, order, and patient identification at the bedside. A critical component to this process includes the patient participation in verifying their identity. This is especially important given studies that have shown an error rate of 2.2% in wristbands from no band to incorrect patient information (9).

Near Misses

One of the positive forces in increasing our understanding of errors and their causes is the increasing encouragement of reporting of near misses, or errors which result in no harm or lesser harm.

The Aviation Reporting System (ASRS) at NASA utilizes confidential incident reports including near misses. The near miss data captured through the ASRS is seen as areas for developing solutions to prevent future occurrences (6).

The Medical Event Reporting System for Transfusion Medicine (MERS-TM) collects, classifies, and analyzes events that potentially could compromise the safety of transfused blood to facilitate system improvement (10). This allows for collection of information including near misses to educate practitioners on causes to prevent future occurrences. Near misses often share similar circumstances and causes as actual serious events and therefore are excellent cases to study in designing systems and processes to reduce the potential for error. While often unrecognized by the provider they occur more frequently then actual errors.

POLICIES

Policies form the framework for safe transfusion practices. While the name may vary by institution—policy, procedure, SOP—the intent is to define the steps necessary to safely carry out a transfusion while minimizing potential known risks. Health care organizations should have well developed policies and procedures to address the following aspects of transfusion medicine.

Storage and Handling of Blood Including Perioperative Area

It is essential that to reduce the probabilities of errors, organizations have well defined policies for the handling and storage of blood products. This ranges from the blood bank, to patient care areas and the perioperative area. Organizations should pay particular attention to the safe storage in perioperative areas including the mixing of units in the same refrigeration system. Time pressures and urgency may lead to improper retrieval. Utilizing the AABB perioperaitve standards and developing SOPs should assist in reducing the likelihood of intraoperative transfusion errors including ABO incompatibilities and patient identification errors.

Informed Consent

The process of obtaining informed consent for transfusion of blood products enables the physician to review with the patient risks and benefits as well as alternatives. This process also serves as a safety net to ensure those who do not wish to receive blood products have the opportunity to refuse. Depending on the location it may also be required legally.

Refusal of Blood or Surgery in a Life-Threatening Situation because of Personal Religious Beliefs and Advance Directives

Policies should address the understanding that all competent adult patients have the right to refuse blood, surgery, and any other medical treatment for personal (religious) reasons. In addition, patients (or appropriate others) have the right to have life-sustaining measures discontinued. If a patient is not competent, then advance directives, health care proxies, or other alternatives should be considered in determining appropriate plan of care.

Treatment of Minors—Refusal of Blood Transfusion(s) for Religious Reasons

One of the more sensitive issues facing physicians and health care providers in transfusion medicine is the approach to treatment of minors who refuse or whose parents/guardians refuse transfusion based on religious reasons. Organizational policies must be consistent with the laws of the particular state. However, and perhaps most important, organizations should have well thought-out policies that will assist in decision making in the event they are confronted with such cases.

At a minimum, organizational policies should acknowledge the potential for conflict between treating physicians and the parents/guardians of children whose beliefs forbid the use of blood transfusions. Policies should address that the hospital staff will always demonstrate sensitivity to the wishes and concerns of the parents/guardians. Parents/guardians will be fully informed of and involved in all actions taken on behalf of a child under the organization's care. An example of such a policy can be found in Table 16.2.

MINIMIZATION OF IATROGENIC BLOOD LOSS

One of the simpler ways organizations can minimize iatrogenic blood loss is by standardizing the usage of phlebotomy tube sizes and educating staff on the appropriate quantity of blood to sample thereby avoiding excess loss of blood, particularly in the intensive care setting. Particular attention should be paid to minimizing standing orders for blood drawing that may increase the iatrogenic blood loss.

TABLE 16.2
POLICY TREATMENT OF MINORS—REFUSAL OF BLOOD TRANSFUSION(S) FOR RELIGIOUS REASONS

Englewood Hospital and Medical Center (EHMC) acknowledges the potential for conflict between treating physicians and the parents/guardians of children whose beliefs forbid the use of blood transfusions. It is the policy of the Medical Center that the hospital staff will always demonstrate sensitivity to the wishes and concerns of the parents/guardians. Parents/guardians will be fully informed of and involved in all actions taken in behalf of a child under our care.

It is the policy of EHMC to encourage all physicians on the medical staff to take all available actions to prevent the need for blood transfusions for all children. However, we will also take into consideration the special circumstances presented by some, such as Jehovah's Witnesses, who refuse blood transfusions for their children due to religious beliefs or medical reasons.

In these specific cases it is the policy of EHMC to adhere to the following protocol:

1. Determine if the parent/guardian and the medical team will execute the form UNDERSTANDING REGARDING REFUSAL OF BLOOD TRANSFUSIONS (See Attached Form).
2. In all cases every effort shall be made to minimize blood loss by coordinating and minimizing testing. This is especially true in dealing with neonates.
3. Review non-blood medical alternatives and treat the patient without using blood transfusions (whole blood, red cells, white cells, platelets, or blood plasma).
4. Consult with other doctors at EHMC who are experienced in non-blood alternative management and treat the patient without using blood transfusions (whole blood, red cells, white cells, platelets, or blood plasma). A list of doctors in The Bloodless Medicine and Surgery Program may be obtained by contacting the Medical Connection (Ext. 3456) or the Program Coordinator of The Bloodless Medicine and Surgery Program (Ext. 3653 or page through Hospital Operator).
5. Contact the Hospital Liaison Committee for Jehovah's Witnesses for their assistance in locating experienced and cooperative doctors at other facilities to consult on alternative care. A list of committee members is available through the Program Coordinator (Ext. 3653).
6. Steps to be taken if alternative care cannot be provided by attending physician:
   a. Transfer the patient to another physician within EHMC, **OR**
   b. Transfer the patient to a physician at another facility who is willing to accept the case.

Where indicated, transfers should be expedited **BEFORE** the patient's condition deteriorates.

7. If in an urgent/emergency situation where the treating physician deems blood transfusion necessary, he/she may report the parental refusal to permit blood to the local child welfare authorities. Before this is done, the parent(s)/guardian and Administration will be notified (Ext. 3002 or page the Administrator on call. On nights or weekends, contact the hospital operator and ask for the Director of Quality Management and also the Bloodless Medicine and Surgery Program Coordinator by long-range pager). This will allow for the due process of law.
8. If, during the course of treatment, a true emergency suddenly arises which allows no time to report the matter to child welfare authorities, the medical team will still do its best to honor the parent(s)/guardian's refusal and treat the child without blood. However, if in such a situation the treating physician(s) deem blood immediately necessary to save the child's life, the law permits them to administer blood notwithstanding the refusal of the parent(s)/guardian, and blood may be administered.

Englewood Hospital and Medical Center

UNDERSTANDING REGARDING REFUSAL OF BLOOD TRANSFUSIONS—MINORS

To:_____, parent(s)/guardian(s)

Of:_____

(Minor Child)

1. The Medical Center acknowledges your directive that no blood transfusions be administered to your child under any circumstances. If you have not already done so, please inform the treating physician immediately. Your directive will be placed on your child's medical record for the medical team's attention.
2. In elective treatment where the physician deems blood transfusion is likely or necessary, your refusal to permit blood may result in the cancellation of treatment.
3. In urgent/emergency medical care when the treating physician deems blood transfusion necessary, he or she may report your refusal to the local child welfare authorities. Physicians may be required to do so by law. However, the Medical Center will use its best efforts to notify you immediately if any such report is contemplated.
4. If, during the course of treatment, an emergency arises which allows no time to report the matter to child welfare authorities, the medical team will still do its best to honor your refusal and treat your child without blood. However, if in such a situation the treating physicians deem blood immediately necessary to save your child's life, the law permits them to administer blood notwithstanding your refusal, and blood may be administered.

_____ _____

(For Medical Team) (Date)

I/We have read and understand what is stated above. Regarding point 4, my/our signing of this statement should be construed only as an acknowledgement of my/our awareness of what the law may provide for in an emergency. It should not be viewed in any way as authorization for a blood transfusion, nor as relinquishing any of my/our rights by law to decide and control what medical care should or should not be administered to my/our child.

_____ _____

(Parent/Guardian) (Relationship to Patient)

_____ _____

(Parent/Guardian) (Relationship to Patient)

_____ _____

(Witness) (Date)

_____

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TABLE 16.3

POLICY: RELEASE OF BLOOD FROM BLOOD BANK, THE NEW JERSEY INSTITUTE FOR THE ADVANCEMENT OF BLOODLESS MEDICINE AND SURGERY

Purpose:

To establish a policy for avoiding the unintended release and subsequent administration of Whole Blood, Cells, Platelets, and Plasma to patients of the Jehovah's Witness faith, or patients who are enrolled in the Bloodless Medicine and Surgery Program at Englewood Hospital and Medical Center. This policy will also address the issue of patients who may choose to accept blood transfusions after previously refusing them and documenting such.

Principles and policy:

Members of the Jehovah's Witness faith do not accept the transfusion of allogeneic whole blood, red cells, white cells, platelets, fresh frozen plasma, or pre-deposited autologous blood. Most will accept albumin, cryoprecipitates, clotting factors, and immunoglobulins, and other cell or plasma derived components on a case-by-case basis. Such wishes are well documented by an advance directive in the chart and must be respected by healthcare providers, regardless of the circumstances.

Other patients, who are not Jehovah's Witnesses, may also refuse blood transfusion, regardless of the possible outcome or circumstances. Such also become part of the Bloodless Medicine and Surgery Program and have their refusal documented in an advance directive format.

It is the law and the policy of Englewood Hospital and Medical Center to respect patient's informed choices regarding the refusal of the use of blood products in their care. Every effort must be made to uphold such wishes, even when patients are impaired, unable to speak, or unconscious.

Policy

Procedure:

I. All patients, whether Jehovah's Witnesses or otherwise, who refuse the transfusion of blood (whole blood, cells, and plasma) under all circumstances, must complete an advance directive which documents such wishes upon admission to Englewood Hospital and Medical Center.
II. This advance directive will be completed after thorough education from and with assistance of bloodless program personnel.
III. Such advance directive will address patient's wishes regarding other blood products (albumin, cryoprecipitates, immunoglobulins, clotting factors).
IV. Patients who are Jehovah's Witnesses will be identified as JHW on their addressograph plate, and as JHW in the religion field of their TDS record AND as BLOODLESS PROGRAM patients in the allergy field of their TDS record.
V. Patients who are not Jehovah's Witnesses, but who refuse blood transfusion, will be identified as BLOODLESS PROGRAM patients in the Bloodless Program field of the TDS system.
VI. A list of all Jehovah's Witnesses patients as well as Bloodless Program patients will be forwarded to the Blood Bank on a daily basis.
VII. The Blood Bank Staff will be notified of each new admission into the Bloodless Program immediately upon the Program's awareness of such admission.
VIII. If a physician orders a blood transfusion (whole blood, cells, and/or Fresh Frozen Plasma {FFP}) for a patient who is identified as one of Jehovah's Witnesses and/or as a Bloodless Program Patient, blood bank staff should contact the nursing unit for clarification. If the transfusion order still stands, the blood is NOT to be released without notification and confirmation of the Bloodless Program Coordinator on-call.
IX. If a patient chooses to accept blood products after previously refusing them, or chooses to rescind an advance directive instruction, such may be done verbally or in writing. If a patient verbally expresses such a change in wishes to a healthcare provider, such wishes must be witnessed and documented in the patient's medical record. The Bloodless Program Coordinator will make notification to the Blood Bank of the cancellation of the Advance Directive as soon as possible.
X. The Bloodless Program Coordinator is available 24 hours a day at XXXXXX.
XI. If no response, the Medical Center page operator has additional backup phone numbers for contact. If the coordinator(s) cannot be reached, the nursing supervisor should be paged.

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Release of Blood from Blood Banks

To ensure patients who do not wish to receive blood products whether for religious reasons or because of personal choice, organizations must have safety mechanisms in place to prevent unintended release and subsequent administration of whole blood, cells, platelets, and plasma. An example of such a policy is shown in Table 16.3

Policies addressing circumstances surrounding the emergency release of blood products should also be defined.

ROLE OF RESEARCH

In reviewing literature related to hospital blood utilization and quality control it is evident that there is more research

needed to enable practitioners a greater understanding of best practices as it relates to this topic. Transfusion medicine research must include a greater understanding of the causes of errors. Uniform definitions and reporting may aid in a greater understanding of blood utilization practices and best practices in quality control.

Health care is experiencing increasing pressures from a myriad of sources including payors, consumers, regulators, and providers themselves. Recently, quality outcomes have received increasing scrutiny and public disclosure from payor groups as well as regulatory bodies (e.g., JCAHO, CMS). Economic incentives for releasing data are emerging. Many states are increasing mandatory reporting requirements for serious adverse events as well as encouraging voluntary reporting of near miss.

The alignment of such reporting requirements and uniformity of definition while fostering a non punitive environment will provide a framework for sharing of knowledge and reducing the potential for error and harm.

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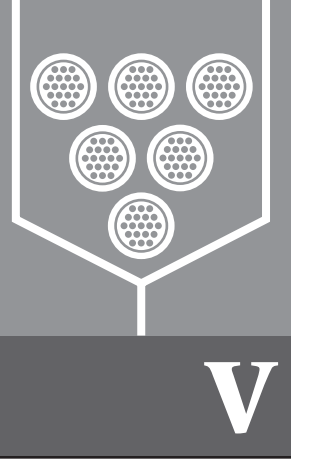
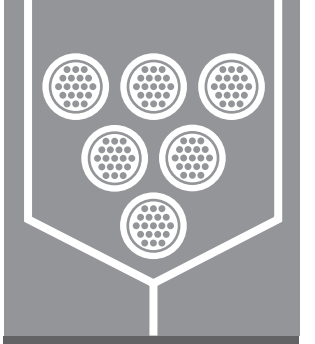


V

Alternatives to Allogeneic Blood



Preoperative Autologous Donation

17

F. Mercuriali G. Inghilleri Richard K. Spence

This chapter is dedicated to the memory of our dear friend and colleague, Francesco Mercuriali, MD. All of us in the field recognize that Francesco was a pioneer in the field of perioperative transfusion medicine with his groundbreaking work on autologous donation. Those of us who were lucky enough to call him a friend, knew him for his warmth and delighted in his intellect, will miss him.

Blood donation and transfusion practices have been dramatically affected by recent changes in the medical and public perception of risks and benefits of blood. Allogeneic transfusion traditionally had been considered as an effective therapeutic intervention, but the fear of contracting blood-borne infectious diseases has fostered an attitude of regarding allogeneic blood transfusion as an outcome to be avoided. Although the current blood supply is safer than ever owing to improved donor screening and testing (1,2), allogeneic blood transfusion still involves the risks of transfusion error, immunological modifications, (3–6) and disease transmission (7–9). Moreover, the introduction of stricter criteria for blood donor selection has further decreased the availability of donor blood for transfusion leading to the adoption of strategies to save this precious, limited, and perishable resource, such as a strict observance of the Maximum Surgical Blood Order Schedule (MSBOS) for the requests (10) and a reassessment of the indication for blood transfusion (11).

The use of donor blood in surgery can be substantially reduced by the introduction of autologous blood (AB) transfusion programs. In many countries, an increase of the use of AB has been documented (1–14).

Transfusion of AB, when possible, is the preferred form of blood replacement for elective surgery (15). Techniques used to obtain AB include preoperative AB donation (16,17), acute normovolemic hemodilution (ANH), (18,19) and perioperative salvage (20,21). A range of techniques is required because the suitability of a given AB transfusion strategy varies with the clinical situation (16,22,23). Preoperative autologous blood donation (PABD) is an attractive way to obtain AB because it is simple to perform, relatively economical, and safe in most patients scheduled for elective surgery; moreover, when correctly utilized, it has been demonstrated to significantly reduce the use of allogeneic blood. As a result, PABD programs have become increasingly popular among patients and are viewed as a standard of care by many physicians, who share the public's concern about the risks of allogeneic blood and are anxious about legal liability (23,24). Anesthesiologists practicing in Germany reported that PABD was the most frequently used form of transfusion alternative in the year 2000 (25,26).

However, the need for allogeneic blood cannot be completely avoided with PABD because low baseline Hct or the development of anemia induced by PABD may prevent the donation of sufficient units of autologous blood. Recently recombinant human erythropoietin (rHuEPO) has been approved for use in surgery as it has been demonstrated that it is effective in increasing a patient's red blood cells (RBCs) production in a short period before surgery. As a result, the amount of autologous blood that can be collected is increased prior to surgery and anemia is corrected preoperatively, so that patients with a low baseline hematocrit (Hct) can participate in PABD programs (27). Moreover, it has been shown that rHuEPO, in properly selected patients, can reduce blood transfusion requirement (28).

In the last few years, however, a great deal has changed. The improvement in the safety of allogeneic blood together with the current pressure on cost-containment has provoked a debate on the utilization of PABD (29–31). Consequently, to define the precise role of PABD alone, or in combination with rHuEPO, in modem transfusion practice, it is necessary to consider all the issues that must be addressed in assessing any form of patient therapy: need,

feasibility, safety, efficacy, and cost-effectiveness. The aim of this chapter is to provide an answer to these questions and to define a rational approach to the utilization of PABD in order to obtain the best results at the lowest cost.

NEED

Despite reduction of the risk of transmitting viruses such as HIV, HBV, and HCV (8,30,31), transfusion of AB remains safer than that of allogeneic blood; therefore, it is appropriate for properly selected patients (32,33). Beside avoidance from transmission of blood-borne infectious disease, AB transfusion prevents noninfective problems induced by allogeneic blood that can cause substantial morbidity, although rarely death (34). Febrile, allergic, and delayed hemolytic transfusion reactions may complicate postoperative care and prolong hospitalization. Alloimmunization may render it difficult and more expensive to find compatible blood for a patient in the future. More serious complications, such as transfusion related acute lung injury (TRALI) and transfusion-associated graft-versus-host reaction or posttransfusion purpura are rare, but their true incidence is unknown. Immune suppression (35) induced by allogeneic blood has been recognized for a long time, but it is still unclear whether this phenomenon, claimed to predispose patients to postoperative infections (6) or earlier cancer recurrence (36,37), is clinically important for all surgical patients.

The medico–legal aspect is another factor to be considered in the judgment of the value and cost-effectiveness of PABD. Therapies that are clearly efficacious but are thought to be costly can be restricted; but patients can be expected to take legal action in the European Union if the only reason for limiting therapy is its cost. A decision to limit AB transfusion because of its high cost is difficult to defend, because it is unquestionably effective in preventing many of the risks of donor blood. However, if it is true that physicians have a fiduciary responsibility to their patients they also have a role as members of the society to conserve limited health care resources (38–40). In many countries, AB transfusion is addressed by specific laws. In these countries physicians are required not only to weigh transfusion risks and expected benefit before prescribing a transfusion but also to inform patients of all transfusion options including autologous transfusion. They are required to schedule nonurgent surgical procedures far enough in advance to allow the ability to utilize alternatives such as PABD or to treat correctable anemia. Such laws currently exist in Italy, France, Germany, Spain, and a number of states in the USA (25,26).

A further important reason for promoting alternatives is that the demand for blood is increasing. The population is getting older and the incidence of pathologies requiring major surgery (orthopedic, cardiovascular, and cancer surgery) with high transfusion requirements has dramatically increased. In the U.S., surgery accounts for more than 70% of red blood cells units collected (41), and in Canada 60% of the 720,000 units annually transfused are utilized, mainly in orthopedic and cardiovascular surgery (42). Moreover, the drastic measures adopted to increase the safety of donor blood reduce the number of active donors making it more and more difficult to fulfill the increasing demand of blood while increasing the cost per unit.

Despite all the measures to limit blood loss, dependency on a consistent blood supply from donors will remain a problem. Consequently, whenever possible and indicated, it is necessary to adopt all the strategies to conserve allogeneic blood in order to offer to the patients a safer transfusion support and at the same time to contribute to the self-sufficiency of the blood supply.

FEASIBILITY

Two different issues characterize the feasibility of a procedure: (a) how large the patient population is that could receive it, and (b) how difficult it is to perform. The data obtained from the great number of PABD programs running all over the world demonstrate that PABD can be performed in a large group of patients. Any patient undergoing an elective surgical procedure for which cross-matched blood is requested is a potential candidate for PABD. It has been estimated that, with a good organization, more than 60% of the patient candidates for major elective surgery can predeposit their blood before surgery.

PABD has become standard practice in orthopedic surgery (42,43), most commonly for elective hip, knee, femur, and spinal surgery. In a 3-year audit conducted in 1,680 patients scheduled for elective orthopedic surgery, the use of PABD increased from 7% of eligible patients in the first year to nearly 50% in the last year. Moreover, in the final year, allogeneic blood transfusion was used in 41% of patients who did not take part in PABD, compared with only 14% of patients participating in a PABD program ($p<0.01$). Overall, 73%, 63%, and 44% of patients undergoing elective hip, knee, and spinal surgery, respectively, chose to predeposit AB during 1990 (43).

In our Institute (Orthopedic Institute of the University of Milan, Italy), where an autotransfusion program with the integrated use of PABD and perioperative salvage has been set up since 1982, between 60% and 70% of all the patients undergoing orthopedic elective surgery could predeposit their own blood (Fig. 17.1). The most frequent reason (24%) for not performing PABD was the presence

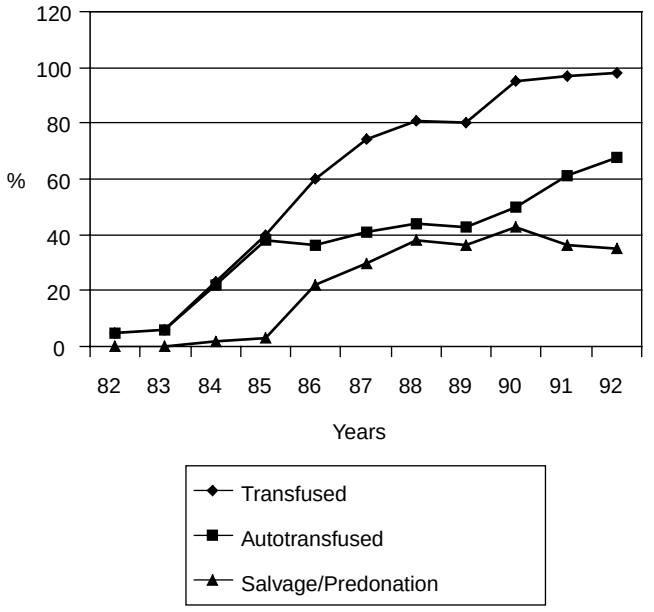


Figure 17.1 Enrollment through the years into the autotransfusion program of the patients undergoing major elective surgery at the Gaetano Pini Orthopedic Institute.

of a clinical contraindication including anemia (4%), cardiovascular diseases (6%), poor general conditions with or without anemia (13.5%), or sepsis (0.5%). Logistical or organizational reasons precluded enrolment in 6% of the cases.

The technical aspects of PABD are straightforward. Moreover, blood bank operators are familiar with PABD as an autotransfusion technique because in many respects it resembles normal allogeneic blood donation. However, both the clinical results obtained and the cost-effectiveness of the procedure depend on the quality of the hospital organization and the cooperation between the different hospital components involved in the procedure.

SAFETY

Although AB donors have more complex medical problems than normal blood donors, the donation process is generally without consequence, and the majority of patients (60% to 70%) are suitable for PABD (32,42–44). The most frequent complications of AB donation are vasovagal reactions (45–47), which consist of self-limited lightheadedness due to transient hypotension and bradycardia. The reaction rate in those who undergo PABD may be similar to or slightly higher than that encountered in first time voluntary donors. These results have been confirmed in a study carried out in our Institute. The reaction rate observed in 4,669 AB donors was slightly higher than that observed in 4,702 periodic donors (4.5% versus 1.5%). No significant difference was observed between autologous donors meeting allogeneic donor criteria versus those who did not (4.1% versus 5.2%, respectively). Severe reactions with loss of consciousness or seizures are uncommon (48,49), although Popovsky et al. (50) reported a significantly higher rate of severe reactions requiring hospitalization in autologous than in allogeneic donors (1:17,000 versus 1:200,000 donors).

Moreover, while blood donation by healthy individuals is regarded as almost without risk, the same may be not true for PABD in patients with significant systemic diseases. Age per se does not represent a contraindication. PABD can be performed in children; however, the volume of blood to be collected at each donation should not exceed 10% of blood volume (usually 6 to 7 mL per kg body weight). Venous access and emotional tolerance to venipuncture could be limiting factors to PABD in children. Some groups of patients, particularly those with cardiovascular disease, may not tolerate the hypotension and bradycardia associated with vasovagal reactions, and are at risk of severe predonation morbidity (such as myocardial infarction or stroke). Although several studies (48–50) reveal that patients with stable heart disease can donate AB safely, other authors (51,52) indicate that PABD may be associated with increased risks in patients with unstable angina, cyanotic congenital heart disease, severe aortic stenosis, and occlusive cerebrovascular disease. It seems wise to perform phlebotomy in these patients only in specialized hospital settings where complications can be attended to promptly.

Autologous blood collection has a quantifiable risk that approaches the risk of viral transmission, particularly in patients with cardiac diseases. This consideration has generated a conflict between a medical condition that discourages blood donation and legal consequences of denying access to a procedure that is mandated by law in several countries (53–55). This conflict must be resolved through a process of informed consent (56,57) in which the relative risks and benefits of all the strategies for blood conservation are explained to the patient.

The final responsibility to establish suitability for PABD lies with the physician who actually performs blood collection. However, patients may not actually be evaluated medically by the doctor in charge of phlebotomy at the transfusion center, especially in the United States. Therefore, protocols or guidelines must be in place to exclude all the medical conditions that contraindicate the donation or the storage of blood. Patients in whom the likelihood is great that no blood transfusion would be required, such as pregnant women, those whose medical condition increases the potential for adverse reaction to blood donation such as cardiovascular patients, and those in whom the risks of a delay

in surgery may be more detrimental than the now quite small risk of acquiring an infection via allogeneic transfusion should be advised against donating their blood. Real time consultation between the ordering physician and the donor center physician are mandatory in such patients.

RISKS OF AUTOLOGOUS TRANSFUSIONS

The transfusion of AB is not without risk. It is free of reactions (allergic, febrile, and hemolytic) but not free of errors in the process of testing, labeling, and transfusing (58). Autologous blood also is subject to the same deterioration and storage lesion found in allogeneic blood. An American Association of Blood Banks autologous survey detected a number of management problems that resulted in transfusion errors, particularly when blood was collected at a regional center and transferred to the hospital for transfusion. Fewer problems occur when AB is collected and transfused in the same hospital. However, there are rare case reports of infection transmitted by AB, so patients should be observed closely even when transfused with AB.

The majority of clerical errors in transfusion are due to a lack of adherence to blood component administration policy and procedures. This observation supports the role of extensive quality assessment/quality improvement (QA/QI) programs in transfusion practice as an effective means also to reduce the incidence of transfusion errors in the transfusion of AB (58). To reduce phlebotomy and bedside identification errors, a device, based on the forcing function concept, was proposed by Wenz and Burns (59). The system (Bloodloc Safety System, Novatek Medical Inc., Greenwich, Conn.) consists of a coded locking system so that a blood unit cannot be accessed without matching a three-letter code that can be found only on the patient's wristband. Any error in patient or blood unit identification would make it impossible to open the lock, and consequently to transfuse the patient. All the errors are automatically referred to the transfusion center, which facilitates both the analysis of all errors occurring in the transfusion process and a concurrent implementation of the QA/QI program in the bedside transfusion practice.

In the Gaetano Pini Orthopedic Institute the Bloodloc Safety System and the associated QA/QI program in transfusion practice were implemented in January 1993 with the aim of preventing bedside transfusion errors and prospectively documenting and quantifying all errors occurring outside the blood transfusion service (60). The system was effective in preventing potentially fatal errors and it has been confirmed that it fits in with the usual protocol for allogeneic and AB transfusion.

Efficacy

The efficacy of an AB technique is measured in terms of enrollment of the appropriate patients and reduction of the use of allogeneic blood. A number of studies in U.S. and Europe seem to demonstrate that PABD is effective in reducing the patient's exposure to allogeneic blood in orthopedic, (61,62) cardiovascular, (63–65) and cancer surgery (66–68). An analysis carried out in more than 10,000 surgical patients transfused in our hospital from January 1990 to June 1995 showed that the utilization of PABD allowed the avoidance of allogeneic blood transfusion in 72.6% (3,432/4,669) of predepositing patients. Only 19.6% (1,077/5,493) of the patients who could not predeposit their own blood and utilized only perioperative salvage as a source of AB accomplished this goal (69). In another large hospital-based program (70), among the 179 patients out of a total of 263 (68%) in orthopedic surgery that successfully predonated the number of units corresponding to the MSBOS, only 17 (9.5%) received allogeneic transfusion while 84 (32%) mainly female patients, unable to predeposit the requested number of units, were transfused with allogeneic blood. In our Institute the use of PABD, integrated with intraoperative salvage, allowed the conservation of a relevant number of blood units (Fig. 17.2). In 1998, 73% of all the blood units transfused to our elective surgery patients were autologous (48% predeposited and 27% salvaged).

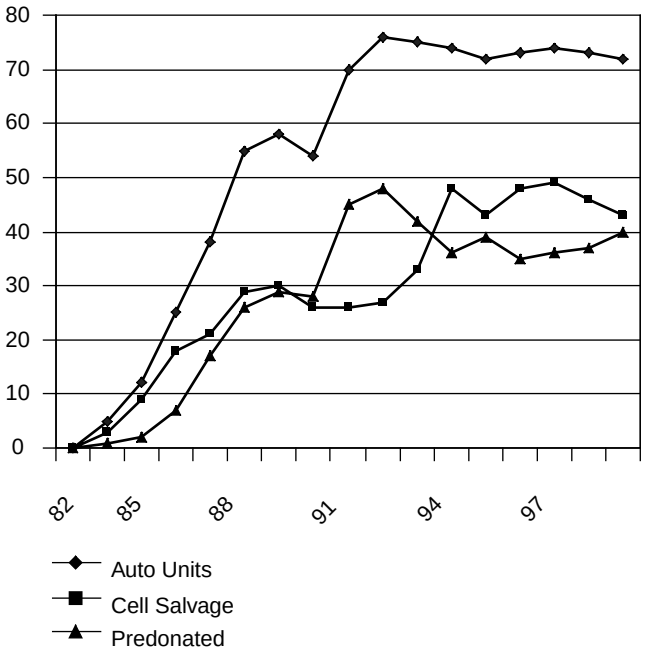


Figure 17.2 Autologous blood units transfused through the years in elective surgery patients at the Gaetano Pini Orthopedic Institute.

However, AB donors undergoing various type of elective surgery have been reported to have a 9% to 27% likelihood of receiving allogeneic blood in addition to their own blood (71). Reported rates of additional allogeneic blood transfusion are 10% for radical prostatectomy (67), 17% for elective orthopedic surgery (64), and 56% for patients undergoing coronary revascularization (72). The analysis of allogeneic blood exposure in 231 patients undergoing primary total hip arthroplasty by Billote et al. (73) showed that although one half of AB donors (22/142, or 15%) avoided allogeneic blood compared to nondonors (29/89, or 33%) ($p < 0.05$), the high rate of breakthrough allogeneic exposure remained a concern. A multicenter study of spinal surgery patients reported that 20% of those who predonated received additional allogeneic blood (74).

The ability of the patient to donate sufficient blood depends on two variables: the total volume of circulating red blood cells (RBCs) which in turn depends on baseline hematocrit, sex and body mass, and the capacity of the patient to reconstitute the RBCs collected at each donation. A baseline hematocrit below 34% not only precludes the possibility of predonation but also significantly affects the quantity of blood that can be donated. Each unit of AB (350 to 450 mL) collected results in a mean decrease of one g per dL of hemoglobin or 3% of hematocrit (75) Collection of three units of blood reduces the Hct by about 10%. Consequently, in patients with a baseline Hct below 39% to 40% this value drops below threshold value for donation of 34% after the collection of the first or second unit (76).

We analyzed the preoperative data from 2,183 PABD orthopedic surgery patients in our Institute to define the distribution of the baseline Hct values. Patients were subdivided into different classes according to the baseline Hct value, the underlying disease condition, and the need for surgical intervention (Table 17.1). Eighteen percent of all patients had a baseline Hct lower than 34% that prevented PABD, and 46% had baseline Hct values between 34% and 40%. The latter group was at high risk of allogeneic blood transfusion when undergoing major orthopedic surgical procedures with expected transfusion need of two to three units. Only 36% of the analyzed patients had optimal baseline values (higher than 40%). As expected the incidence of low baseline Hct values varied significantly according to the underlying disease: up to 25%, 30%, and 42% of the patients had a baseline Hct <34% in rheumatoid arthritis, cancer, or sepsis group, respectively. By contrast, the incidence of such a low value was 35% in a group of trauma patients, e.g., hip fracture (77).

Thus, according to the analysis, approximately one fifth of patients undergoing major orthopedic surgical procedures were not candidates for PABD. Almost one half of the group were unable to complete a planned predonation schedule because they reached the cutoff 34% Hct after initial PABD. The administration of recombinant human erythropoietin (rHuEPO) may be a valuable adjunct in these patients to increase the efficacy of all the autotransfusion techniques (78,79).

PABD patients must be able to recover from the predonation phlebotomy, which depends on an inadequate stimulation of endogenous erythropoietin (EPO) production induced by repeated blood donations. However, the rate of bone marrow erythropoietic activity is normally only slightly increased after the collection of AB units. Although an increase from baseline EPO values occurs, the increase is generally not above the normal upper limits (80). Several

TABLE 17.1

DISTRIBUTION OF THE BASELINE HCT VALUES IN 2183 PABD ORTHOPEDIC SURGERY PATIENTS BY SEX AND DIAGNOSIS FROM GAETANO PINI INSTITUTE

	20.5–29.96%	30–33.9%	34–39.9%	40–55.9%	Total
N Pts	129	252	1,010	792	2,183
% of total	6	12	46	36	
Female	99	203	931	389	1,522
Male	30	49	179	403	661
Osteoarthritis	19	70	624	585	1,298
Rheumatoid arthritis	6	16	42	19	82
Cancer	14	17	39	33	103
Sepsis	8	16	17	16	57
Trauma	78	126	264	113	581
Other	4	8	24	26	62

studies have shown that the endogenous erythropoietin response is suboptimal at the level of mild anemia achieved during collection of AB (81). Relationship between the degree of anemia and EPO is linear only in anemic patients with Hb values less than 10 g per dL, which are rarely if ever reached in patients enrolled in autotransfusion programs.

For the patients clinically suited for PABD, a low baseline initial Hct value and anemia induced by the collection of blood units constitute a significant hindrance to donating the amount of AB required to cover perioperative and postoperative transfusion requirements (81). In view of this, it was suggested that recombinant human EPO (rHuEPO) could be used to stimulate erythropoiesis in such patients. The aims of rHuEPO therapy are to increase initial Hct levels to permit PABD and to accelerate the reconstitution of red cells lost during collection so that the phlebotomy-induced anemia. The increase of baseline Hct would enable patients with low Hct to be enrolled in a PABD program, to tolerate a greater perioperative blood loss and to predeposit a higher volume of AB (82,83).

ROLE OF RECOMBINANT HUMAN ERYTHROPOIETIN (RHUEPO) IN SURGERY

Erythropoietin (EPO) is the erythroid hormone primarily produced by the kidney in response to hypoxia. Hypoxia induces a rapid increase in renal production of the hormone through an exponential increase in the number of EPO-producing cells according to a classic negative feedback control system (84). EPO is the primary regulator of erythropoiesis and exerts its effect by binding to a surface receptor on an erythroid progenitor and precursor. Receptor expression decreases with erythroid maturation and in the peripheral reticulocytes is practically undetectable. EPO acts both as a survival factor and a mitogen (85). Enhancement of cell replication, however, is observed on mutated cell lines only when EPO is combined with stem cell factor (86). For normal erythroid progenitors with high receptor number (CFU-Es and erythroblasts) EPO is mainly a survival factor by repressing apoptosis (87).

Recombinant human erythropoietin (rHuEPO) became available for clinical trials in 1985. The efficacy of rHuEPO in increasing the collection of AB patients undergoing major elective surgery was first shown in a randomized placebo-controlled study (88). It was demonstrated that patients who received 600 VI per kg of rHuEPO biweekly for 3 weeks donated a 41% greater volume of RBCs than placebo-treated patients. So far, numerous clinical studies have been carried out and published on the effect of rHuEPO on AB donation and on erythropoietic stimulation prior to surgery. These studies included healthy volunteers, heart surgery patients, and orthopedic patients (88–94). In all the clinical studies considered, rHuEPO was found to be effective in stimulating erythropoiesis, with a consequent increase in the volume of red cells produced during the course of treatment and in the number of units predeposited. It was also effective in correcting anemia induced by collection of blood units.

However, despite the mass of data collected, it proved initially difficult to draw conclusions on the use of rHuEPO in autotransfusion programs because the data from the different studies were difficult to compare as a result of the range of protocols used. The protocols differed in terms of the clinical characteristics of patients enrolled, the type of surgery undergone, the use of different rHuEPO administration protocols, and the type of iron treatment (dose, method of administration). Considerable differences were also noted among criteria used in assessing the efficacy of the treatment, specifically the effect of rHuEPO on erythropoietic stimulation and consequent expansion of the circulatory red cell mass. Other assessment criteria include the reduction in use of allogeneic blood and exposure to transfusion risks, interpreted as an increase in the proportion of patients able to satisfy their transfusion requirement solely using AB or the reduction in the number of allogeneic units transfused.

Evaluation of the Efficacy of rHuEPO in Increasing the Volume of Predeposited Blood

In all the clinical studies considered, rHuEPO was found to be effective in stimulating erythropoiesis, with a consequent increase in the volume of RBCs produced during the course of treatment and in the number of units predeposited. It was also effective in correcting anemia induced by blood collection. Although the volume of new red cell production was found to vary considerably (250–900 mL), the amount of blood deposited by patients treated with rHuEPO was always significantly higher than that deposited by the control group. The extent of the increase seems to correlate fairly well with the amount of rHuEPO administered (95). The most common treatment protocol used involved the intravenous (IV) administration rHuEPO twice a week for 3 weeks together with oral iron supplementation. The total dose of rHuEPO administered varied from study to study. It was found that total doses of less than 600 IU per kg were ineffective in promoting sufficient erythropoiesis to significantly increase the volume of blood the patient was able to predeposit. High doses, on the other hand, gave rise to a dose-dependent production of new red cells ranging from 350 mL for total doses of

600 IV per kg to more than 900 mL for doses of 3600 IV per kg. The limit above which no further increase in response is observed seems to fall when iron is administered intravenously (iron sucrose at a dose of 100 mg whenever rHuEPO is administered) (95).

Another cause of variation is the route of administration. Some authors who used the subcutaneous (SC) route (96–101), obtained results comparable with the results obtained by IV administration yet used lower drug doses. One author (96) compared a total IV dose of 1,400 IU per kg with a SC dose of 1,200 IV per kg achieving the same degree of hemopoietic stimulation. The results of this study were nevertheless affected by the fact that the iron treatment was administered in a different way in both cases: orally in the case of patients treated with SC rHuEPO and IV for patients treated with IV rHuEPO (96). We performed a pilot study at our institute to find out whether subcutaneous administration of rHuEPO at doses (800 IU per kg) lower than those used previously for intravenous administration (1,800 IU per kg) was equally safe and effective. The study was carried out on 22 rheumatoid arthritis patient candidates for total hip knee replacement who were unsuitable for inclusion in the predeposit program due to anemia (hematocrit less than 34%). The results obtained were compared with those obtained from a group of patients matched by age, sex, duration, and stage of rheumatoid disease who underwent the same type of operation carried out by the same surgeon.

Patients enrolled in the study received 100 IU per kg of rHuEPO given SC twice a week for 3 weeks plus a 200 IU per kg IV bolus of rHuEPO at the time of the first administration of the drug (total dose 800 IU per kg) [II patients] or 300 lU per kg intravenous rHuEPO twice a week for 3 weeks (total dose 1,800 IU per kg) [II patients]. All patients received IV iron therapy during the course of drug treatment. Subcutaneous administration of a dose 55% lower than the IV dose was found to be equally effective in terms of the average number of units predeposited (2.6 + 0.9 versus 2.6 + 0.6), volume of autologous erythrocytes deposited (291 + 99 mL versus 366 + 98 mL), mL red cells produced during treatment, and average reticulocyte peak (5.0 + 1.7% versus 3.8 + 0.9%). The average number of allogeneic units transfused per patient in the group treated SC was similar to that for the IV group (0.3 + 0.8 and 0.8 + 0.8, respectively).

Reduction of Allogeneic Blood Transfusion

Although the increased availability of AB would imply reduced use of allogeneic blood, in most of the early studies no clinical benefit was detected in patients treated with rHuEPO, as a difference in allogeneic blood transfusion was not observed between placebo-treated and rHuEPO-treated patients. This is essentially due to the fact that transfusion treatment in surgical patients is subject to numerous variables dependent on the patient's clinical condition, the type of surgery, the skill of the surgeon, the surgeon's thoroughness in ensuring hemostasis, and also the transfusion policy.

Another difficulty met when interpreting data in the literature is the fact that, in many studies, patients undergoing different types of surgery with different transfusion requirements have been enrolled in the same study. Moreover, in multicenter studies transfusion treatment can be affected by the different transfusion policies adopted and by differences in the surgical and anesthesiological techniques used. However, the most important reason for lack of demonstration of the efficacy of rHuEPO in reducing allogeneic blood transfusion is that most of the patients enrolled in the early clinical trials had high basal Hct levels and some were candidates for surgical procedures with low transfusion requirements. In these patients an aggressive phlebotomy program (two units of blood per week) has been proven to supply sufficient blood to meet requirements for the majority of surgical procedures without utilizing rHuEPO (97), Moreover, patients with high Hct values can tolerate greater intraoperative blood losses than anemic patients for the same operation. The inclusion of patients with high hematocrit values in these studies made it difficult to show the efficacy of rHuEPO in decreasing the exposure to allogeneic transfusion.

We retrospectively reviewed the transfusion treatment of our patients, correlating the number of units actually predeposited by the patients to the baseline Hct value before donation to define the critical Hct value below which the patients would receive the greatest benefits from rHuEPO treatment (90). Patients with baseline Hct values less than 37% predeposited zero to one unit, which was generally insufficient to cover their transfusion need. When Hct values were between 37% and 40%, AB donations covered transfusion requirement in approximately 56% of cases. Patients with Hct values higher than 40% could predeposit three or more units of blood. Female patients had lower values of Hct and lower body mass than males and were exposed to a greater risk of allogeneic transfusion. We concluded that only patients with an Hct lower than 40% scheduled for surgery with an expected transfusion requirement equal to or greater than three units should be enrolled in studies aimed to demonstrate the efficacy of rHuEPO in reducing allogeneic blood use.

In studies where these selection criteria have been adopted, IV administration of rHuEPO 300 UI per kg twice a weekly for 3 weeks facilitated AB donation and reduced the need for allogeneic blood in patients with low Hct (101,102). We applied the protocol proven to be effective

in the previous study (rHuEPO 300 VIU per kg given IV in combination with IV administration of 100 mg of iron sucrose, twice a week for 3 weeks) (103) in 11 rheumatoid arthritis (RA) patients with severe anemia of chronic disease (ACD) who were surgical candidates and were unable to donate AB because of anemia (Hct <34). In this study rHuEPO was shown to be safe and effective in stimulating erythropoiesis, allowing the preoperative collection of AB and reducing the exposure to allogeneic blood in these highly compromised patients. In a similar U.S. study, allogeneic blood transfusion was required in 31% of placebo-treated patients, compared with 20% of rHuEPO-treated patients (104). Although this difference did not reach statistical significance, rHuEPO-treated patients did demonstrate the ability to donate significantly more autologous units (4.5 units per patient versus 3.0 units per patient for placebo; $p < 0.001$) and significantly increased RBC production (688 ml versus 353 mL for placebo; $p < 0.05$). These studies have shown that rHuEPO therapy, with adequate iron supplementation, can make PABD a successful option for many anemic surgical patients who would otherwise need allogeneic transfusion. The use of rHuEPO is effective in optimizing the efficacy of ANH and in significantly reducing allogeneic blood exposure in patients undergoing surgery (105–107). Also, rHuEPO has been successfully used in surgical patients in whom compatible allogeneic blood transfusion was difficult because of the presence of multiple red cells alloantibodies (108,109).

A particularly important issue to be solved in the clinical application of rHuEPO in surgery is the high cost of the treatment. Goodnough et al. (101) demonstrated in a randomized trial of PABD versus ANH that both alternatives produced comparable outcomes in allogeneic blood avoidance, but PABD was more expensive than ANH. The addition of rHuEPO to PADB only adds to the expense. Cost-effective use of rHuEPO requires identifying and using the lowest effective dose needed to supplement PABD. A dose–response relationship between rHuEPO dose and production of new RBCs has been reported in AB donors with normal Hct and in patients with low baseline Hct value (110–112). In a trial carried out in our institution 40 patients with Hct <39% were assigned to receive IV rHuEPO 75 UI per kg, 150 UI per kg or 300 UI per kg or placebo, twice weekly for the 3 weeks prior to surgery (112). All patients were supplemented with IV iron sucrose (200 mg) administered in conjunction with rHuEPO. A dose-dependent increase in the mean number of AB units donated was documented with a significant difference between the 300 UI per kg group and the placebo group ($4.3 + 0.9$ versus $2.1 + 1.1$ units; $p < 0.05$). A similar increase was observed for mean total RBC volume donated ($526 + 118$ mL and $276 + 169$ mL in the 300 UI per kg and placebo groups, respectively; $p < 0.05$).

Since studies have demonstrated that the SC route of administration may allow lower dosages of rHuEPO to be used we conducted an open-label pilot study in 24 anemic patients (Hct <34%) with rheumatoid arthritis prior to total hip or knee replacement. Patients received IV rHuEPO 300 UI per kg IV or 100 UI per kg SC biweekly for 3 weeks. Patients in the 100 UI per kg group also received an IV bolus dose of 200 UI per kg at the first visit. All patients received IV iron sucrose 200 mg at each of the six visits prior to surgery and donated one unit of AB (350 mL) when Hct was >34%. The results of this study demonstrated that the SC administration of a total dose of 800 UI per kg is as effective as the IV administration of a total dose 1,800 UI per kg in allowing PABD, stimulating erythropoiesis, and reducing allogeneic blood needs in patients with Hct <34% who would otherwise have been unable to initiate an AB donation program.

A number of factors, such as infection, inflammation, malignancy, aluminum overload, or secondary hyperparathyroidism, may result in a suboptimal marrow response to rHuEPO. However, depletion of iron stores is the most important and most common cause of the failure of rHuEPO treatment. Iron plays an essential role in erythropoiesis and Hgb synthesis. One hundred fifty mg of stored iron is required to increase circulating Hgb by one g per dL (111). Thus, it is important to include some form of iron supplementation during treatment with rHuEPO, when the rate of erythropoiesis (and hence iron mobilization) is accelerated.

The importance of iron supplementation during rHuEPO administration was first demonstrated in patients with chronic renal failure (CRF), in whom a suboptimal response to rHuEPO was associated with insufficient iron availability (110). The results of these studies suggest that the oral administration of iron in patients with CRF is not sufficient to deliver an adequate amount of iron to optimize rHuEPO-stimulated erythropoiesis. Indeed Van Wick (112) recommends prophylactic oral iron supplementation (ferrous sulfate 325 mg twice daily) in patients without evidence of iron overload and the use of IV iron when oral administration is not sufficient to meet the demand of rHuEPO-accelerated erythropoiesis. In patients enrolled in an AB donation program, iron depletion appears to be even more critical in determining the response to rHuEPO than in patients with CRF. This may be due to the higher dosages of rHuEPO administered over a shorter time period. In these patients, the severity of iron deficiency varies according to the magnitude of pretreatment iron stores, the rate of increment of Hgb values and by the volume of RBCs collected. Moreover, as more than 60% of the

total body iron is located in RBCs, patients with low Hgb levels have lower than normal content of total body iron, even with normal iron stores. Oral iron supplementation may therefore not provide sufficient iron to optimize rHuEPOaccelerated erythropoiesis.

Indeed, the route of iron supplementation represents a significant variable in the erythropoietic efficacy of rHuEPO in patients donating AB prior to elective surgery, as shown by a study performed in 50 female patients with a baseline Hct <39% scheduled for hip replacement surgery (113). All patients received oral iron supplementation (elemental iron 125 to 270 mg per day) and were treated with rHuEPO 300 IU per kg or 600 IU per kg IV twice weekly for 3 weeks prior to surgery. In the first 24 patients enrolled, rHuEPO was associated with a significant ($p < 0.05$) increase in reticulocytes 1 week after the commencement of treatment, an interval compatible with the time required for the maturation of erythroid precursors. The response, however, was blunted after the second or third rHuEPO dose, and the reticulocytes either stabilized at 3% or dropped back to baseline values. The only parameter that correlated with this observation was a concomitant drop in iron parameters to below normal values. This was particularly marked in patients with baseline ferritin levels lower than the 50% of the normal distribution (52 ng per mL).

Accelerated erythropoiesis during treatment with rHuEPO can therefore lead to a *functional* iron deficiency, i.e., adequate stores of iron cannot be mobilized quickly enough to support the demands of the erythroid marrow. Thus, the quantity of iron absorbed following oral administration may not be sufficient to fulfill the needs of accelerated erythropoiesis, thereby preventing the production of new erythrocytes. For these reasons, we started rHuEPO treatment in the remaining 24 study patients in our study only when baseline serum ferritin levels were adequate, that is, greater than 52 ng per mL. Patients received IV iron (iron sucrose 100 mg IV twice weekly) in addition to oral iron supplementation (elemental iron 270 mg per day). This protocol was associated with enhanced reticulocytosis throughout the rHuEPO treatment period, and all rHuEPO-treated patients predeposited >4 AB units. Furthermore, the mean volume of RBCs predonated by patients treated with IV iron was significantly higher than that of patients treated with oral iron (643 + 127 mL versus 454 + 133 mL; $p < 0.05$). The different routes of iron supplementation also affected the exposure to allogeneic blood transfusion. Fewer patients receiving IV iron required allogeneic blood compared with patients treated with oral iron (16% versus 36%).

Iron emerged as a critical factor during rHuEPO administration study performed by Brugnara et al. (114) in healthy volunteers donating two units of AB a week for 3 weeks. SC treatment with rHuEPO (200 IU/kg/day) significantly increased ($p < 0.05$) mean RBC production, although the mean Hct decreased during the donation period. Despite normal baseline iron stores and use of oral iron supplementation, iron stores fell significantly ($p < 0.05$) during the donation period and the depletion of iron was hastened by rHuEPO administration. Moreover, treatment with rHuEPO was associated with the production of RBCs of low Hgb content, which appeared in the circulation in advance of laboratory evidence of depletion of iron stores. The authors concluded that the rate of erythropoiesis and total normal iron stores and oral iron supplementation are not sufficient to sustain rHuEPO-induced erythropoiesis. Feagan et al. (115) used oral iron supplementation in their randomized trial of two doses of rHuEPO in hip replacement patients but did not attribute any specific difference in outcome to its use. In order to maximize the beneficial effects of rHuEPO, it is mandatory to identify those patients who already have an iron deficiency, in order to correct their iron status before starting rHuEPO therapy to support increased erythropoiesis during the treatment. In our institute when at least one of the parameters utilized to evaluate the patient's iron stores is below the 75th percentile of the normal distribution (i.e., serum ferritin <100 ng per mL, serum iron 120 mg per mL transferrin saturation <20%) we administer from 500 to 1,000 mg of elemental iron as iron sucrose in four to five daily doses before starting rHuEPO treatment, 200 mg of elemental iron are administered by slow IV infusion at each donation visit.

Undesirable Effects of rHuEPO in Surgical Patients

The incidence of side effects in patients treated with short-term preoperative rHuEPO is low and does not differ significantly from that observed in patients within the placebo group in all studies examined. The only complication in a setting where a great number of patients have been enrolled utilizing different doses and protocols and have been monitored for a long period is chronic renal failure. Hypertension was a serious and frequent complication of rHuEPO treatment. In early studies in uremic patients but this was attributed to the too rapid correction of anemia, which induced a significant increase in blood viscosity and a reversal of vascular hypotonia (116–117). Hypertension did not occur more frequently in rHuEPO patients than in controls in the studies cited above. It appears that short-term treatment with rHuEPO, as carried out in surgical patients, does not pose a significant threat of hypertension.

The incidence of deep vein thrombosis associated with rHuEPO treatment has been analyzed in different studies. Two orthopedic studies (118,119) documented a higher incidence of deep vein thrombosis, as detected by ultrasonography or venography. In one study, however (118), the incidence was higher only in patients with high Hgb values (>13 g per dL) while in patients with Hgb values between 10 and 13 g per dL the occurrence of deep vein thrombosis was similar to that of the patients in the placebo group. Two different doses of rHuEPO were used (600 and 300 IU per kg weekly) in the second study (119). The incidence of thrombosis was 5% in the group receiving 600 IU per kg and 0% in the 300 IU per kg group. The meta-analysis of data by De Andrade (120) from four prospective multicenter randomized studies involving 869 major elective orthopedic surgery patients showed that the incidence of thrombotic/vascular events was similar between 619 patients treated with Epoetin alfa and 250 patients receiving placebo (7.4% versus 8.0%, respectively). He concluded that the use of rHuEPO did not affect the probability of thrombotic/vascular events.

The increase in blood viscosity due to the accelerated expansion of circulating RBCs mass could be responsible for rHuEPO-associated thrombosis. However, Tobu et al. (121) believe that thrombosis in patients with end-stage renal disease may be due to increased expression of C-reactive protein (CRP) as a result of chronic inflammation. Chronic inflammation also promotes the release of thrombin activatable fibrinolytic inhibitor, which causes a fibrinolytic deficit that leads to thrombosis. Increased viscosity is generally not a problem when rHuEPO is associated with PABD because of the scheduled phlebotomy that lowers Hct. However, the chronic inflammation of rheumatoid arthritis may be related to an increased risk of thrombosis if the above theory is correct.

Of greater concern about the importance of increasing viscosity, however, are the results obtained in a study on patient candidates to coronary artery by-pass grafting (122). Seven out of 126 (5.5%) preoperatively treated with rHuEPO without PABD died, while no deaths occurred in the 56 patients of the placebo group. Although the death rate in these 256 cases of the rHuEPO group is comparable to that reported in the literature for similar patients in the waiting list for coronary artery bypass grafting, four out of the seven deaths were associated with thrombotic or vascular events so that an effect of rHuEPO cannot be completely excluded.

The effect of rHuEPO is also specific for erythropoiesis. No other significant changes have been noted in any other cell types or any modifications in any of the blood chemistry parameters considered. In some cases, an increase in platelet number has been observed, but the values have never exceeded the upper limits of normalcy and in any case, the levels returned to initial values 4 to 5 days after suspending drug treatment (123).

COST-EFFECTIVENESS

The cost- effectiveness of a medical intervention is defined by the ratio of its cost and its expected health benefit (124), where benefit would be defined as the intervention's impact on longevity and/or quality of life. This concept of cost-effectiveness requires the definition of a measure for cost-effectiveness, such as the cost per quality-adjusted life-year saved (QALY) (125,126). A number of studies attempted to define this value for PABD. These studies seem to indicate a poor cost-effectiveness for PABD but the results could not be considered conclusive because these studies showed striking difference in the costs between the centers considered (varying from 5,000 U.S. dollars to 32,500,000 U.S. dollars) and the questionable methodology used to calculate the cost of QALY (127,128). However, it can be observed that PABD becomes less cost-effective as soon as the safety of allogeneic blood supply increases.

Moreover, PABD is considered more costly than allogeneic blood (128) as patients require a greater input of medical staff time. The assessment for fitness to donate has to be individualized and nursing attention is increased as many patients are both elderly and first-time donors. Clerical workload is also increased because of the need for cooperation between surgeon, blood bank anesthetist, and theater staff. Moreover, as AB can only be used for the patient who donates it, wastage rates are higher, averaging 40% in most studies. If the cost of rHuEPO is added to the cost of PABD, the ratio between cost and benefits is further reduced.

However, given the value of AB for patients and its ability to reduce exposure to allogeneic blood transfusion, the practice of PADB is not likely to be abandoned because of its economic implications. Thus every effort should be made to render both the practice of PABD and the utilization of rHuEPO more cost-effective in order to guarantee autologous transfusion to the patients who need it. This can be accomplished through different measures such as the reduction of the costs of blood collection, the optimization of efficacy of PABD and rHuEPO treatment, the selection of patients, and the avoidance from collection of unnecessary AB units.

Reduction of the Costs of Blood Collection

A number of strategies have been suggested to reduce the cost of PABD.

Optimize Organization and Scheduling

An optimal organization to make patient selection, evaluation and scheduling as automatic as possible is mandatory. In our institute we evaluate patient suitability for intervention before hospital admission. If crossmatch blood units are requested for a procedure, we determine the appropriateness of the order according to a continuously updated MSBOS. Once the patient's suitability for the operation has been confirmed, he or she is automatically referred to the blood transfusion service and is evaluated for eligibility to be enrolled in the autotransfusion program (PABD alone or in combination with rHuEPO, treatment of correctable anemia).

STREAMLINING OF THE AUTOLOGOUS BLOOD DONOR INTERVIEW

Contrary to allogeneic blood donors in whom the majority of questions are intended for the protection of the recipient, in autologous donation, questions can be limited to those important to the safety of the donation process; moreover, the questions addressing the safety of the blood supply can be limited to the possibility of bacterial contamination. In our institute a specific questionnaire has been developed that includes only 10 questions requiring approximately 5 minutes to complete compared with the 15 minutes required to complete the questionnaire for the allogeneic donor that includes more than 50 questions.

Discontinuation of Serologic Tests for Infectious Disease Markers

FDA requirements for autologous units shipped between institutions are that at least the first of the units collected in a 30-day period from a donor-patient be tested for HIV, HCV, and HBV surface antigens and for syphilis, while testing is optional for AB units used within the collection facility. In other countries it is compulsory to perform the full array of tests used for allogeneic blood in all AB collected. Since marker-positive blood need not be discarded and unused AB components collected for PABD are not crossed over, the rationale and the utility for performance of these expensive tests is unclear and probably unnecessary (129). The probability of transmitting HIV or hepatitis with autologous units given erroneously to the wrong patient as the result of a clerical error can be calculated to be in the area of 1 in 120,000,000 transfusions (taking into account a 1:10,000 risk for HIV positive donor (130) and a 1:12,000 risk for transfusion of the wrong unit). The risk might be higher when prospective studies on the frequency of bedside transfusion errors that report error in the 1:155–2,748 per transfusion range are taken into account (131). In our setting, disease marker testing is not routinely performed and we believe that the requirement for infections marker testing of AB should be abandoned. However, it is reasonable to institute systemwide processes aimed to avoid transfusion errors (132).

Use of Single Collection Bags in CPDA-1

Since fresh frozen plasma and platelets are rarely, if ever, needed in elective surgery, we avoid the fractionation of autologous units (133).

Optimization of Efficacy of PABD

The production of new RBCs throughout the PABD program depends on many variables such as the patient's baseline Hct, the underlying disease, and the interval between the first donation and the day of surgery. In our experience, the main factor influencing the volume of new RBCs produced is the time interval between the collection of AB units and surgery. Studies have shown that patients scheduled for cardiac surgery can donate three to four units of blood over a 4-week interval (134) but this result has been not confirmed in other studies performed in patients undergoing hysterectomy (135), radical prostatectomy (136), or colectomy (137).

Indeed, in a study carried out in 11 female patients with optimal hematological conditions who predeposited three units of AB in 10 days, it was observed that at least 15 to 20 days after the collection of the first units were necessary before a consistent production of new RBCs is obtained (Figure 17.3).

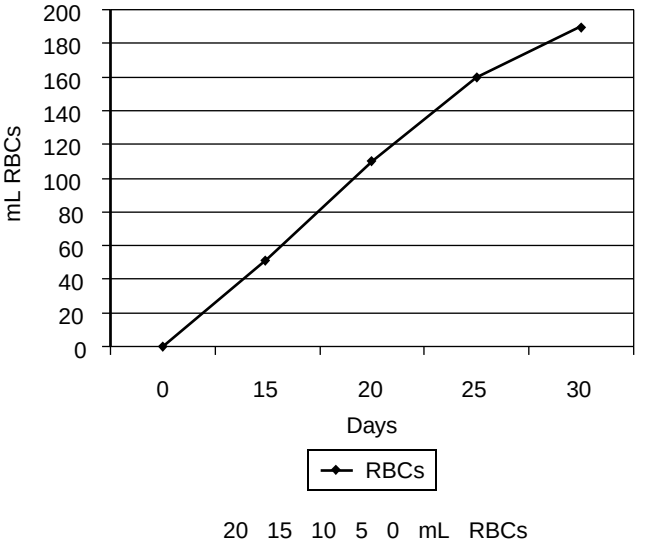


Figure 17.3 Production through the days of new RBCs after the donation of three units of AB in 11 female patients.

TABLE 17.2
COMPARISON OF RESULTS ATTAINED IN TWO GROUPS OF PATIENTS PREDEPOSITING THREE UNITS OF AB IN 7 DAYS OR IN 15 DAYS. MAIN CLINICAL PARAMETERS AND TOTAL RBCS PRODUCTION IN APPROXIMATELY 30 DAYS

	3 Days	7 Days
Number	0	80
Age	58.9 ± 7.8	59.6 ± 9.7
Body weight (kg)	65.5 ± 10.7	67.0 ± 11.6
Predicted blood volume (L)	3.83 ± 0.4	3.89 ± 0.5
Baseline Hct (%)	40.5 ± 2.7	39.1 ± 2.2
Preoperative Hct (%)	35.7 ± 2.7	34.4 ± 2.3
Interval Baseline-Preop (days)	25.9 ± 4.7	25.6 ± 4.1
RBC production (mLs)	258 ± 130	262 ± 208

The interval between collection (138) seems to have less influence on the patient's erythropoietic activity than the number of AB units collected, The volume of new RBCs produced by a group of 40 patients who predeposited three AB units in 7 days (collection every 3 days) and a group of 80 patients who predeposited the same number of AB units in 15 days (collection every 7 days) was similar. (Table 17.2).

Our analysis of 358 candidates for total hip replacement showed that in a period of 29 + 5 days, patients who predeposited one AB unit produced 94 + 78 mL of RBCs. Production increased to 175 + 100 mL of RBCs in patients predepositing two units and reached 238 + 13 mL of RBCs in the patients from whom two or more AB units were collected. These data indicate that the degree of iatrogenic anemia induced by phlebotomy plays a major role in determining the stimulation of erythropoiesis even if the patient's Hct remains above 30%. Indeed, when the results obtained in patients are subdivided according to the baseline Hct, it can be observed that when two or more units of AB are collected, patients with baseline Hct <40% produce more RBCs than those with a baseline Hct >40 (Table 17.3). Based on these findings, we concluded that the patient needs at least 15 days after the donation of at least two units of AB to obtain a net recovery of 200 mL of new RBCs.

Avoidance of Wastage from Collection of Unnecessary AB Units

Wastage of PABD units must be avoided. Part of the wastage is due to the fact that more than 20% of AB units may be collected for surgical procedures in which the transfusion likelihood is less than 10% (138). Autologous blood collection should be limited to surgical procedures in which the need for blood transfusion has already been clearly established. Lists of surgical procedures for which PABD, alone or in association with rHuEPO, is indicated or not indicated have been published by different scientific societies and are available in literature (138,139). However a reasonable and practical approach to be adopted is to create in each hospital a list of surgical procedures suited for PABD based on the local MSBOS. Patients who are candidates for an operation in which the probability of allogeneic transfusion is less than 10% should be discouraged from PABD. In procedures where PABD is appropriate, collection in excess of transfusion needs, i.e., collection to above the mean, should be kept to a minimum.

For many years, we have utilized the Schedule of Optimal Preoperative Collection of Autologous Blood (SOPCAB) suggested by Axelrod et al. (140) to define the

TABLE 17.3
TOTAL RBCS PRODUCTION (ML OF RBC) IN APPROXIMATELY A 30 DAYS PERIOD IN PATIENTS ENROLLED INTO THE PABD PROGRAM SUBDIVIDED ACCORDING TO THE NUMBER OF UNITS PREDEPOSITED AND THE BASELINE HCT VALUE

N Units Predonated	Baseline Hct (%)	N Pts	Mean mLs ± SD
1	<40	23	81 ± 72
	≥40	37	101 ± 81
2	<40	80	200 ± 76
	≥40	13	7161 ± 110
3	<40	36	264 ± 125
	≥40	45	217 ± 99

number of units to be collected from the donor-patient. SOPCAB takes into account both intraoperative and postoperative blood requirements (number of blood units—autologous and allogeneic—transfused to each patient throughout the entire hospital stay for each surgical procedure). Ideally it is equal to the number of units of AB sufficient to avoid completely the exposure to allogeneic blood in at least 80% to 90% of the patients. In our setting MSBOS and SOPCAB have been updated periodically as perioperative transfusion practices have changed. By adopting these strategies, we have kept the overall wastage of AB below 15% and of allogeneic blood below 3%. Since undercollection of blood may be hazardous, we have accepted a higher risk of allogeneic blood exposure of 10% to 20% for elderly patients than for young patients undergoing spine surgery (Table 17.4).

We have experimented with a new and more personalized approach (141) to PABD that defines both the perioperative blood requirement and the utilization of all the methods to cover the calculated blood requirement for a specific patient. This new approach takes into account the predicted blood loss determined through a constantly updated calculation of the real blood loss that occurred in each patient per surgical operation and the volume of the blood loss that the patient can tolerate before needing a transfusion support. The tolerated blood loss depends on the circulating RBCs mass. Young patients in good clinical condition can safely tolerate low Hct/Hgb values (21% to 24% Hct), while those who are elderly or suffer from cardiovascular or respiratory diseases affecting oxygen delivery to the tissues should be maintained at higher Hct/Hb values (27% to 33% Hct). Both the predicted blood loss for each surgical procedure and the blood loss that a single patient can tolerate can be precisely calculated (in mL of pure RBCs) utilizing appropriate formulas (154). The difference between the predicted blood loss and the blood loss tolerated by the patient represents the transfusion requirement of the single patient expressed in mL of pure RBCs.

When a negative figure is obtained from this difference, it means that the patient can tolerate losing a volume of blood larger than that expected to be induced by the operation the patient is undergoing. In this case PABD is not indicated and a type and screen is ordered. However, as the intraoperative and postoperative bleeding is unpredictable, in order to protect the patient from unexpected high surgical blood loss, perioperative blood salvage is kept on standby. The shed blood is washed and returned only when enough blood has been collected into the reservoir and when the volume of blood harvested is considered clinically useful by the anesthesiologist.

A positive figure obtained from our calculations represents the transfusion need expressed in mL of RBCs. In this case the safest and possibly the most cost-effective transfusion strategy has to be defined to obtain the predicted volume of RBCs to cover transfusion need. The choice of the transfusion strategy to be adopted depends on type of surgery; time to surgery; applicability of the specific autotransfusion techniques; general clinical status of the patient (hematological, cardiopulmonary); and consideration of cost-effectiveness.

To verify the efficacy of the algorithm in selecting patients to be enrolled into the PABD program with or without rHuEPO treatment, we retrospectively applied the algorithm to 577 patients, each of whom predonated two or three units of AB prior to total hip replacement surgery, and subdivided the patients according to the calculated transfusion requirement (71). We observed that only 68%

TABLE 17.4

RESULTS OF THE APPLICATION OF THE MSBOS AND SOPCAB IN THE MANAGEMENT OF THE PABD PROGRAM AT THE GAETANO PINI ORTHOPEDIC INSTITUTE

	N of Cases	N of AB Units to Be Collected (SOPCAB)	Collected Units per Patient	Wasted Units (% Collected)	% of AB Units Transfused
THR	822	3	2.76	101.5	79.5
TKR	120	3	2.35	9.5	76.6
THR revision	91	6	4.1	6	67
Bilateral THR	37	11	10.2	14	89.2
Vertebral arthrodesis	43	5	5.2	15	100

THR, total hip replacement; TKR, total knee replacement.

of the patients avoided the use of allogeneic blood if the calculated transfusion need was greater than 500 mL of RBC (<5% of total evaluated patients), in spite of the utilization of all the currently available autotransfusion techniques. In more than 95% of patients with a calculated transfusion need lower than 200 mL of RBC, allogeneic transfusion was avoided. We also documented overcollection of AB in this group as demonstrated by the wastage of about 20% of the autologous units collected. If we had applied the algorithm for the choice of the most appropriate blood conservation strategies, we could have avoided unnecessary collection of AB in patients with low transfusion requirement, thus saving resources that could have been utilized for a rHuEPO treatment in patients at higher risk to require allogeneic blood transfusion because of low baseline Hct values.

CONCLUSIONS

The risks of allogeneic blood as well as decreasing supplies and increasing costs mandate the adoption of transfusion alternatives. The practice of PABD, although once considered the standard of care in orthopedic surgical patients has advantages and disadvantages. We believe that the former clearly outweigh the latter and support the continued use of PABD to increase benefit and to reduce risk for our patients.

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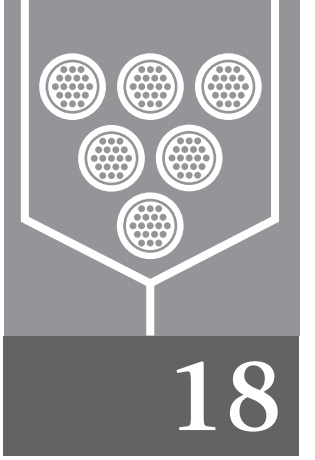

Erythropoietin Therapy

18

Lawrence T. Goodnough

Erythropoietin (EPO), a glycoprotein hormone, is the primary regulator of erythropoiesis. EPO is produced primarily in the kidney in the adult, with a small amount produced in the liver. Under normal physiological conditions, there is an inverse correlation between tissue oxygenation and circulating EPO levels, with kidney hypoxia being the main stimulus to EPO production (1). EPO acts on committed erythroid progenitor cells to stimulate their proliferation and differentiation into mature RBCs.

The purification and amino acid sequencing of human urinary EPO permitted the production of large quantities of EPO in mammalian expression vectors through the use of recombinant DNA technology (2–4). The recombinant human EPO (rHuEPO) produced in mammalian cells is biologically active and biologically indistinguishable from human urinary erythropoietin and is referred to generically as epoetin alfa. A genetically engineered variant is darbopoietin alfa, with two additional sialic acid residues permitting increased carbohydrate content and a longer circulating half-disappearance time (5).

Clinical trials have resulted in approval for rHuEPO (epoetin alfa) as an effective treatment for anemia in a variety of clinical settings, including anemia associated with chronic kidney disease (6), human immunodeficiency virus (HIV) infection (7), cancer (8), and surgery (9). Darbopoietin alfa is currently approved for chemotherapy-induced anemia in cancer patients (10).

Subsequent clinical trials have demonstrated the safety and efficacy of perioperative epoetin alfa for increasing erythropoiesis, and thus RBC mass, and in reducing exposure to allogeneic blood transfusions in patients undergoing major elective surgical procedures (11–14). This chapter reviews the use of epoetin alfa as a perioperative pharmacologic strategy in blood management.

PHYSIOLOGY OF THE ERYTHROPOIETIC RESPONSE TO ANEMIA

rHuEPO in mammalian expression vectors (i.e., epoetin alfa) and EPO purified from human urine have indistinguishable biological activity, along with an identical amino acid sequence and similar, but not identical, oligosaccharide chains. EPO is a glycoprotein with a molecular mass of approximately 30,400 Da, consisting of approximately 30% carbohydrate (15) linked to a polypeptide backbone. This single-chain polypeptide backbone has a sequence of 165 amino acids with a molecular mass of 18,400 Da and two intrachain disulfide bonds that are important for the conformation and biological activity of the molecule (16).

The major functions of EPO are to recruit, maintain, and induce the differentiation of erythroid progenitor cells. EPO is primarily, but not completely, restricted in its target cell specificity to cells in the erythroid differentiation pathway. EPO dependence develops in parallel with expression of the soluble EPO receptor. The burst-forming unit erythroid (BFU-E) and the colony-forming unit erythroid (CFU-E) are the earliest erythroid progenitor cells that demonstrate EPO dependence and peak EPO receptor expression (17). The BFU-E are the most primitive erythroid progenitor cells that respond to EPO and require the synergistic action of EPO with interleukin-3 and/or granulocyte-macrophage colony-stimulating factor to differentiate into a colony of recognizable RBC precursors (18). The CFUE are completely dependent on EPO for proliferation, viability, and differentiation. As differentiation of the erythroid cell line proceeds through the late CFU-E stage, EPO receptors and dependence on EPO decline in parallel (19). The proerythroblast, the progeny of the CFU-E, is the earliest morphologically recognizable RBC precursor in the

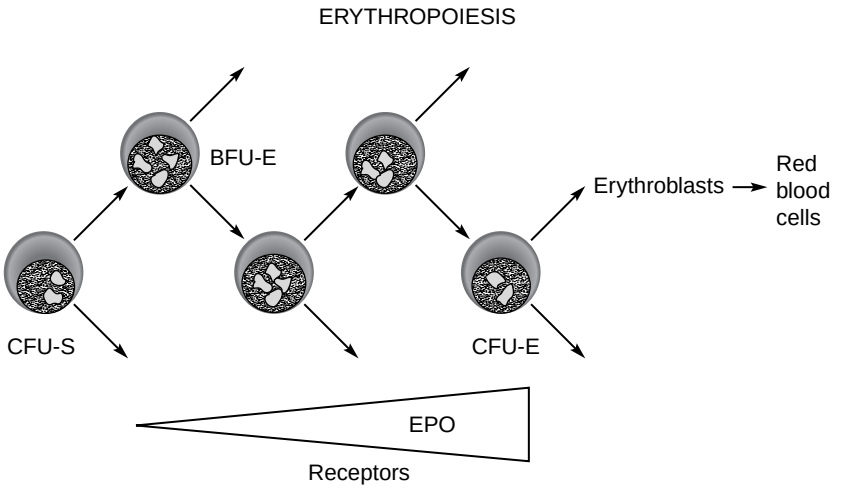

Figure 18.1 The kinetics of erythroid progenitors and their assumed dependence of receptors for erythropoietin. This hormone appears to act as a growth factor for progenitor ells and a differentiation factor for the transformation of CFU-E to erythroblasts. (Adapted from Erslev AJ, Caro J. Physiology and molecular biology of erythropoietin. *Med Oncol Tumor Pharmacother*. 1986; 3:159–164.)

bone marrow and does not appear to require EPO for maturation into the reticulocyte (Fig. 18.1).

In adults, the primary site of EPO production is the kidney (20). However, the identity of the EPO-producing cell within the kidney remains controversial (21). Although the kidney is the major site of EPO production in the adult, the liver is the principal EPO-producing organ in the fetus (22). Small quantities of EPO are produced in the liver in the adult, usually under conditions of renal dysfunction or absence (23).

The regulation of EPO production involves a classic feedback loop (24) (Fig. 18.2). Under normal physiological conditions, there is an inverse correlation between tissue oxygenation and circulating EPO levels, with kidney hypoxia the main stimulus to EPO production. Hypoxia induces increased EPO gene transcription and increased EPO messenger RNA levels, leading to increased production and secretion of biologically active EPO (25).

The increased RBC mass produced in response to increased EPO levels results in an increase in the oxygen-carrying capacity of the blood. This decreases the hypoxic stimulus to the kidney, thereby decreasing EPO production. The linkage between the production and action of EPO in this negative feedback loop maintains the RBC mass at a volume that is optimal for oxygen transport.

Serum EPO levels have been demonstrated to be inversely proportional to hematocrit (Hct) and hemoglobin (Hgb) in anemic patients with normal renal function (25). In individuals with Hgb levels within the normal range, endogenous serum EPO levels range from 5 to 30 mU per mL of

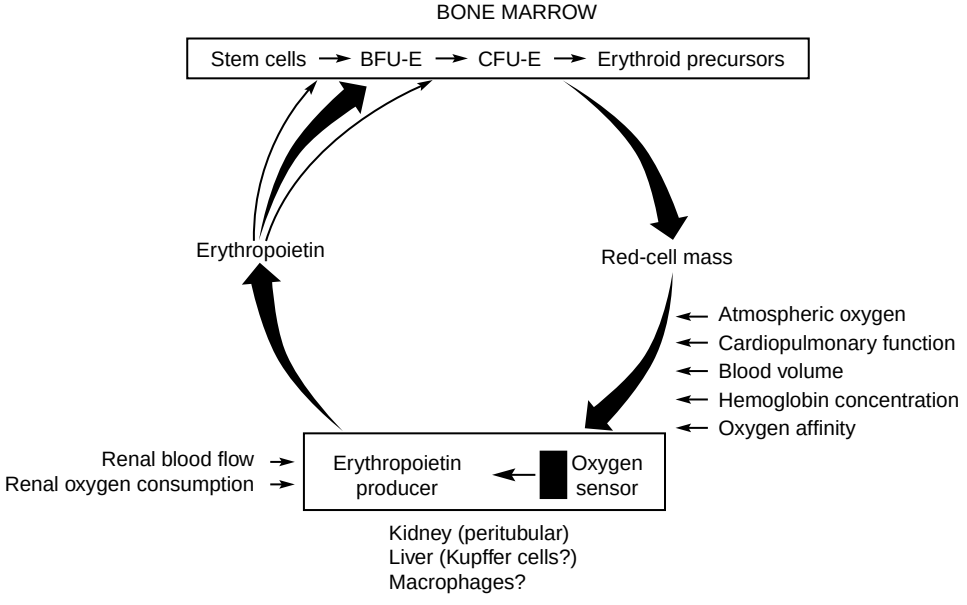

Figure 18.2 The feedback circuit that adjusts the rate of red-cell production to the demand for oxygen. BFU-E denotes burst-forming units–erythroid, and CFU-E colony-forming units–erythroid. (Adapted from Erslev AJ. Erythropoietin. *N Engl J Med*. 1991;342:1339–1343.)

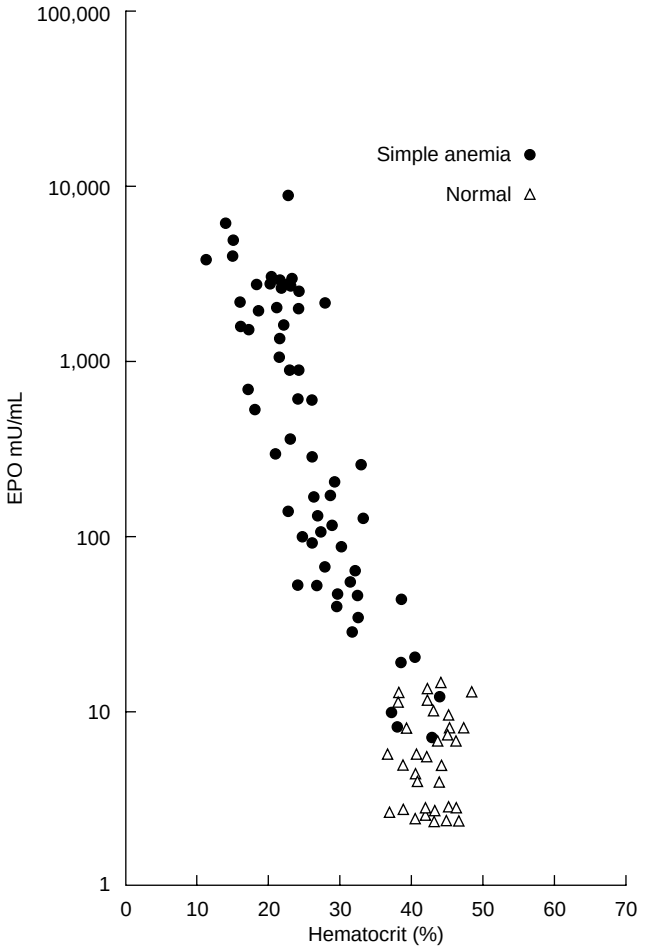

Figure 18.3 Erythropoietin titers in milliunits per ml of plasma in normals and in patients with simple anemias not complicated by renal or chronic disease. The titers were all determined by bioassay in hypertransfused mice. (Adapted from Erslev AJ, Caro J. Physiology and molecular biology of erythropoietin. *Med Oncol Tumor Pharmacother*. 1986; 3:159–164.)

plasma (18). EPO levels increase exponentially in the presence of anemia, and with an Hct less than 20%, 100-fold or greater increases in plasma EPO levels have been observed (Fig. 18.3) (19).

Anemia is a powerful stimulus to EPO production in patients with normal renal function and Hgb-oxygen affinity. However, the anemia that is a consequence of chronic diseases, such as chronic kidney disease, chronic inflammatory disorders, and infectious disorders, does not stimulate production of EPO in quantities sufficient to restore the RBC mass. In patients with chronic kidney disease (26), cancer (27), HIV (28), and rheumatoid arthritis (29), the EPO response is blunted in comparison with that of iron-deficient patients with a comparable degree of anemia.

Effective erythropoiesis results in the incorporation of 80% to 90% of total body iron into Hgb in circulating erythrocytes. Under normal conditions, iron homeostasis is strictly maintained, but a heightened demand for iron due to accelerated erythropoiesis can increase iron absorption and alter iron kinetics. As a consequence, iron availability has been identified as a rate-limiting factor for erythropoiesis. Iron kinetics are closely coupled with the rate of erythropoiesis. A correlation exists between the serum ferritin concentration and body iron stores, with serum ferritin levels providing an indirect measure of the level of tissue iron stores. Serum ferritin levels range from 30 to 250 ng per mL and transferrin saturation between 20% and 45% in normal individuals. In the absence of an accompanying disease, a serum ferritin level of less than 30 ng per mL or a transferrin saturation level of less than 20% indicates iron deficiency (30).

One clinical situation of particular relevance to surgical blood management is the development of mild asymptomatic anemia in patients participating in a preoperative autologous blood donation (PAD) program. A PAD program usually involves the donation of 450 mL ±10% of RBCs every 3 to 7 days, provided that the patient maintains an Hct level greater than 33% (Hgb greater than 11 g per dL) (31). Many donors, however, fail to maintain an adequate Hct during the course of repeated phlebotomy and thus fail to donate sufficient blood to meet operative needs, due to an increase in serum EPO level that is insufficient to stimulate adequate erythropoiesis to maintain RBC mass (32–35).

PHARMACOLOGY OF ERYTHROPOIETIN

Epoetin alfa has been shown to produce a dose-dependent stimulation of RBC production. When administered intravenously to patients with chronic kidney disease, epoietin alfa is eliminated at a rate consistent with first-order kinetics, with a circulation half-life of approximately 4 to 13 hours. The peak serum EPO level is reached within 1 hour. Detectable levels of plasma EPO are maintained within the therapeutic dose range for at least 24 hours (36). In healthy volunteers (37), the half-life of intravenously administered epoetin alfa is approximately 20% shorter than that found in patients with kidney disease. (24,37) (Fig. 18.4).

Subcutaneous administration of epoetin alfa yields a volume of distribution identical to that obtained through intravenous administration. However, the time required to reach peak serum EPO levels is substantially longer in subcutaneous than in intravenous administration, ranging from 5 to 24 hours and declines slowly thereafter, with a half-life of more than 24 hours (24). Peak serum EPO levels reached with subcutaneous administration are significantly lower

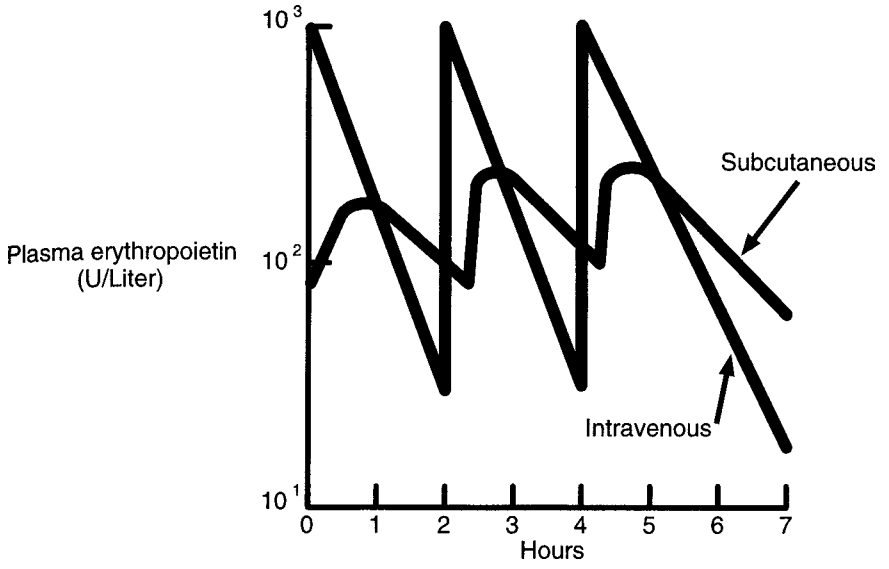

Figure 18.4 Plasma levels of erythropoietin after intravenous or subcutaneous injections of 40 U per kilogram three times a week. (Adapted from Erslev AJ. Erythropoietin. *N Engl J Med*. 1991;342:1339–1343.)

than those after comparable intravenous doses (24,36). A 20% to 30% lower dose of epoetin alfa administered subcutaneously has been shown to provide comparable erythropoietic stimulation with an intravenous dose (37). Thus, subcutaneous administration of epoetin alfa is a more cost-effective route for patients scheduled for major elective surgery.

Normal iron stores, although adequate for basal erythropoiesis, may not be sufficient for the accelerated erythropoiesis associated with epoetin alfa therapy, even with oral iron supplementation (38–40). Clinical observations have indicated that epoetin alfa therapy stimulates significant mobilization of iron stores, so that iron availability becomes a rate-limiting factor for erythropoiesis (30,33,41). Supplemental oral iron is generally poorly absorbed in the gastrointestinal tract. Various preparations have been devised to improve the absorption rate, but at present the maximum reliable absorption rate is approximately 20 mg of elemental iron per day. Using the simplified formula that equates an increase of 1 g per dL Hgb with 200 mg of elemental iron (the equivalent of one blood unit (42)), patients would require 10 days of oral iron supplementation therapy, assuming continual optimum absorption, which is seldom attained.

ERYTHROPOIETIN, IRON, AND ERYTHROPOIESIS

Goodnough et al. (33) summarized knowledge gained regarding the relationship between erythropoietin, iron, and erythropoiesis in patients undergoing PAD in elective orthopaedic surgery (as a model for blood loss anemia), with or without EPO therapy. A summary of selected prospective controlled trials of patients undergoing PAD discussed in the review is presented in Table 18.1. Endogenous erythropoietin-mediated erythropoiesis in response to PAD under standard conditions of one blood unit donated weekly, in this setting generates 397 to 568 mL RBC, or the equivalent of two to three units of blood. Exogenous erythropoietin (EPO) therapy in patients undergoing PAD generates 358 to 1102 mL, or the equivalent of two to five units of blood (Table 18.2). With enhanced erythropoiesis during exogenous EPO therapy, iron-restricted erythropoiesis occurs even in patients with measurable storage iron (43). The superior erythropoietic response in a patient with hemochromatosis further suggests that iron-restricted erythropoiesis occurs in patients receiving EPO therapy (Table 18.2), even with oral iron supplementation.

Erythropoietin Therapy and Erythropoietic Response

An analysis of the relationship between erythropoietin dose and the response in red blood cell production has demonstrated a good correlation (Fig. 18.5), and can be used to determine the appropriate rHuEPO dose to generate the desired increase in red cell mass (44). Erythropoietin-stimulated erythropoiesis is independent of age and gender (45), and the variability in response among patients is in part due to iron-restricted erythropoiesis (43). There is no evidence that surgery or erythropoietin therapy affects the endogenous erythropoietin response to anemia, or the erythropoietic response to erythropoietin (46).

Red blood cell expansion is seen with an increase in reticulocyte count by day 3 of treatment in nonanemic

TABLE 18.1
ENDOGENOUS ERYTHROPOIETIN-MEDIATED ERYTHROPOIESIS

		Blood Removed (Donated)				Blood Produced		
	Patients (n)	Requested/ Donated Units		RBC (mL)	Baseline RBC (mL)	RBC (mL)	Expansion (%)	Iron Therapy
Standard phlebotomy	108	522	2.7	522	1884	351	19	PO
	22	590	2.8	590	1936	220	11	None
	45	621	2.9	621	1991	331	17	PO
	41	603	2.9	603	1918	315	16	PO + IV
Aggressive phlebotomy	30	540	3.0	540	2075	397	19	None
	30	558	3.1	558	2024	473	23	PO
	30	522	2.9	522	2057	436	21	IV
	24	683	4.1	683	2157	568	26	PO
	23	757	4.6	757	2257	440	19	PO

Data expressed as means. PO, Oral; IV, Intravenous.
Adapted from Kickler TS, Spivak JL. Effect of repeated whole blood donations on serum immunoreactive erythropoietin levels in autologous donors. *JAMA*. 1988;260:65–67.

patients treated with EPO who are iron-replete (34). As illustrated in Figure 18.6, the equivalent of one blood unit is produced by day 7 and the equivalent of five blood units produced over 28 days (47). If three to five blood units are necessary in order to minimize allogeneic blood exposure in patients undergoing complex procedures such as orthopedic joint replacement surgery, the preoperative interval necessary for EPO-stimulated erythropoiesis can be estimated to be 3 to 4 weeks.

Normal individuals have been shown to have difficulty providing sufficient iron to support rates of erythropoiesis that are greater than three times basal (48). A recent study confirmed that the maximum erythropoietic response in the acute setting, seen in EPO-treated patients with measurable storage iron, is approximately four times basal marrow RBC production (45). Previous investigators have shown that conditions associated with enhanced plasma iron and transferrin saturation produce a greater marrow response, such as in patients with hemachromatosis (49) or in patients supplemented with intravenous iron administration (50).

In hemochromatosis, marrow response has been estimated to increase by sixfold to eightfold over baseline RBC production with aggressive phlebotomy (49). The term

TABLE 18.2
ERYTHROPOIESIS DURING BLOOD LOSS AND ERYTHROPOIETIN THERAPY

		Blood Removed			Blood Produced		
Patients N/sex	Total EPO Dose (U/kg)	Units	RBC (mL)	Baseline RBC (m)	RBC (mL)	Expansion (%)	Iron Therapy
10/F	900 SQ	3.4	435	1285	358	28	IV
24	900 IV	5.2	864	1949	621	32	PO
10/F	1800 SQ	4.3	526	1293	474	37	IV
26	1800 IV	5.5	917	2032	644	32	PO
11/F	3600 IV	4.9	809	1796	701	39	PO
12/M	3600 IV	5.9	1097	2296	1102	48	PO
23	3600 IV	5.4	970	2049	911	45	PO
18	3600 IV	5.6	972	2019	856	42	PO
1/M	4200 IV	8	1600	2241	1764	79	Hemochromatosis

Data are expressed as means. Adapted from Kickler TS, Spivak JL. Effect of repeated whole blood donations on serum immunoreactive erythropoietin levels in autologous donors. *JAMA*. 1988;260:65–67.

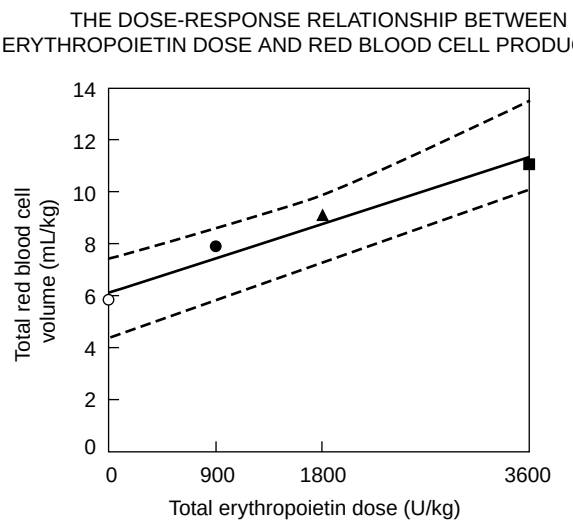

Figure 18.5 The dose and response relationship between total (cumulative) amount of erythropoietin (EPO) administered (units per kg body weight for six treatments over three weeks) and the red blood cell volume increase (mL per kg body weight) during the preoperative interval for patients treated intravenously with placebo, 150 u per kg, 300 u per kg, and 600 u per kg. Doses of erythropoietin are given in total (cumulative) units per kilogram of body weight for all six treatments combined over a period of three weeks; increases in red cell volume are given in milliliters per kilogram of body weight. The dotted lines indicate the 95% confidence interval. (Adapted from Goodnough LT, Verbrugge D, Marcus RE, et al. The effect of patient size and dose of recombinant human erythropoietin therapy on red blood cell expansion. *J Am Coll Surg*. 1994;179;171–176.)

relative iron deficiency has thus been termed by Finch (51) to occur in individuals when the iron stores are normal but the increased erythron iron requirements exceed the available supply of iron.

Iron supplementation with at least 100 mg elemental iron per day taken with food, can cover the increased iron needs from the endogenous erythropoietin response in autologous blood donors (33). However, a randomized trial of erythropoietin therapy found the optimal erythropoietic response was in patients who received intravenous iron supplementation (52). Another study found that for iron-replete patients there is a significant relationship between storage iron and marrow response in patients receiving EPO therapy (45). These results suggest that both storage iron and iron supplementation are important for maintaining sufficient plasma transferrin saturation for optimal erythropoiesis in the setting of erythropoietin therapy.

Iron Therapy

In circumstances with significant ongoing iron losses, oral iron does not provide enough iron to correct the iron-deficient erythropoiesis, and intravenous iron therapy should be considered. Renal dialysis patients have such blood losses, and the role of intravenous iron therapy has been best defined in clinical trials achieving target hematocrit levels in this setting. Addressing iron deficiency with intravenous iron therapy allows correction of anemia along with utilization of lower erythropoietin dosage (53). Another role for intravenous iron therapy is in the arena of bloodless medicine and bloodless surgery programs for patients who refuse blood transfusions on the basis of religious beliefs. Common clinical settings here include pregnancy (54) and patients with dysfunctional uterine bleeding who are scheduled for hysterectomy (55).

Intravenous iron therapy has been closely scrutinized for risks and adverse events. Imferon (Iron Dextran BP) is an iron preparation previously associated with a 0.6% risk of life-threatening anaphylactoid reactions and 1.7% risk of severe delayed reactions that were serum sicknesslike and characterized by fever, arthragias, and myalgias (56). An increased incidence of delayed reactions of up to 30 and severe reactions of 5.3% was subsequently described (57); this product was eventually withdrawn from use.

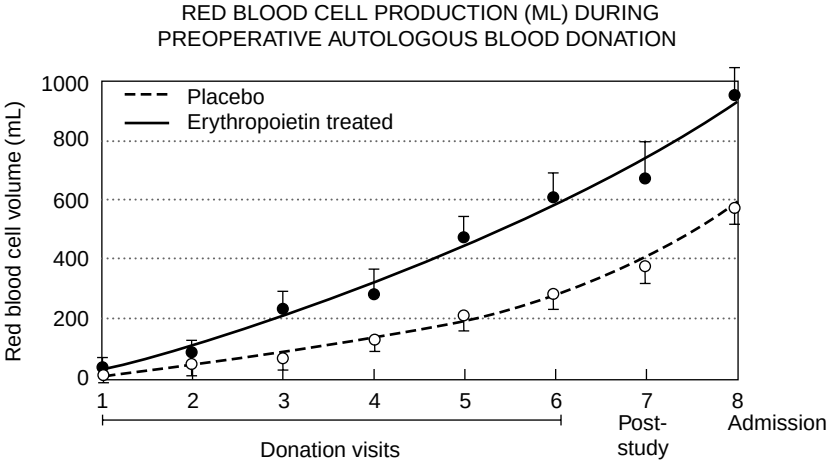

Figure 18.6 Red cell (RBC) production during autologous blood donation, in 23 placebo treated (O) and 21 erythropoietin-treated (O) patients. Data points represent calculated RBC production (mL) at donation visits 1 through 6, the post study visit, and hospital admission. RBC production is indicated by polynomial regression curve for each treatment group (n = 44 at each point). The rate of RBC production can be derived for any preoperative interval. The mean cumulative interval since donation visit 1 was 3.5 days to visit 2, 7.2 days to visit 3, 10.6 days to visit 4, 14.2 days to visit 5, 17.6 days to visit 6, 20.9 days to visit 7 (poststudy visit) and 26.3 days to visit 8 (hospital admission). (Adapted from Goodnough LT, Price TH, Rudnick S. et al. Preoperative red blood cell production in patients undergoing aggressive autologous blood phlebotomy with and without erythropoietin therapy. *Transfusion*. 1992;32:441–445.)

InFed (Iron dextran USP, Schein Pharm Corp, Florham Park, NJ) is currently approved for parenteral (intramuscular or intravenous) use, with widespread intravenous administration in renal dialysis patients. Clinical studies have shown that InFed administered intravenously during the dialysis procedure was associated with clinically significant adverse reactions in 4.7% of patients, of which 0.7% were serious or life-threatening, and another 1.75% were characterized as anaphylactyoid reactions (58). The prevalence of these reactions does not appear to differ among patients receiving low dose (100 mg) or higher dose (250 to 500 mg) infusions (59). A recent review reported 196 allergic/anaphylaxis cases with the use of iron dextran in the U.S. between 1976 and 1996, of which 31 (15.8%) were fatal (60).

Safety aspects of parenteral iron in patients with end-stage renal disease for iron dextran, ferric gluconate, and iron saccharate have been scrutinized (61). Iron saccharate is an available preparation to which allergic reactions are rare. Possible adverse effects include a metallic taste, arthralgia, chest pain, or brochospasm (61–63). Ferric gluconate is an intravenous iron preparation approved for use in renal dialysis patients. Dosage is limited to 125 mg over a 1 hour infusion at each administration (64). The rate of allergic reactions (3.3 episodes per million doses) appears lower than iron dextran (8.7 episodes per million doses) and the safety profile of iron gluconate is substantially better; among 74 adverse events reported as severe reported with its use from 1976 to 1996, there were no deaths (60).

Adverse events that have been reported associated with ferric gluconate include hypotension, rash, chest or abdominal pain, with an incidence of less than 5% (65). Another potential adverse effect of intravenous iron therapy is a clinical syndrome of acute iron toxicity (nausea, facial reddening, and hypotension), which has been attributed to oversaturation (>100%) of transferrin. This has been described with rapid infusion of ferric gluconate (62.5 mg to 125 mg within 30 min) in a study of 20 dialysis patients (66). However, a recent report disputed the existence of this effect (i.e., oversaturation of transferrin) by demonstrating that two laboratory assays for measurement of serum iron yield misleading results for transferrin saturation if performed within 24 hours after infusion (67). Serious reactions including one hypotensive event were reported in only three (1.3%) of 226 patients undergoing renal dialysis while treated with ferric gluconate in one European study (68).

Previous studies (69) have indicated that the increased erythropoietic effect (4.5 to 5.5 times basal) of intravenous iron dextran (with an estimated half-life of 60 hrs) is transient and lasts 7 to 10 days, after which the iron is sequestered in the reticuloendothelial system, and erythropoiesis returns to 2.5 to 3.5 times normal (70). Intravenous iron therapy is therefore recommended to be administered at intervals of 1 to 2 weeks. A dose-response relationship of erythropoietin and erythropoiesis that is affected favorably by intravenous iron, even in iron-replete individuals, has important implications for erythropoietin dosage, (9) especially if the cost of therapy is taken into account. Intravenous iron may potentiate the erythropoietic response in the setting of erythropoietin therapy by improving iron-restricted erythropoiesis induced by erythropoietin therapy.

In summary, perioperative epoetin alfa therapy in patients undergoing major elective surgery has been shown to significantly increase the volume of autologous blood donated before surgery through expansion of the RBC mass. Finally, clinical observations demonstrate that administration of epoetin alfa in combination with a PAD program bolsters pre-PAD Hgb levels in both nonanemic and anemic patients, allowing their entry into a PAD program, prevents PAD-induced anemia, allowing completion of scheduled PAD, and thereby reduces the exposure to allogeneic transfusion.

PERIOPERATIVE ERYTHROPOIETIN THERAPY

Perioperative epoetin alfa therapy has demonstrated significant efficacy in reducing allogeneic transfusion in surgical patients who were unable to participate in a PAD program. Recent clinical trials have demonstrated that treatment with perioperative epoetin alfa alone, without concomitant PAD, reduces the need for allogeneic transfusion in patients undergoing major elective orthopedic surgery. Epoetin alfa has been found to produce a dose-dependent increase in RBC volume before elective surgery in patients who might otherwise have required up to three units of allogeneic blood. The rationale for epoetin alfa therapy is that if RBC mass can be increased preoperatively and the rate of erythropoietic recovery can be increased postoperatively, the RBCs remaining after surgical blood loss should be sufficient to avoid allogeneic blood exposure.

Three major studies have evaluated the use of epoetin alfa as a perioperative adjuvant in 724 patients undergoing major elective surgery (11–13). These studies indicate that compared with placebo, epoetin alfa therapy results in a significantly lower incidence of exposure to allogeneic blood transfusion. Specifically, 300 IU per kg epoetin alfa administered subcutaneously for 10 days before, on the day of, and for four days after surgery results in a significantly lower incidence of exposure to allogeneic blood transfusion compared with placebo in patients with baseline Hgb more

than 10 to no more than 13 g per dL. Epoetin alfa was also well tolerated in this patient population, with a safety profile similar to that seen with placebo treatment.

A randomized, multicenter study found that 600 IU per kg epoetin alfa weekly was at least as effective as 300 IU per kg epoetin alfa daily (14). Therefore, if the period before surgery is at least 3 weeks, 600 IU per kg epoetin alfa may be administered as an alternative dosing regimen once weekly for 3 weeks (e.g., days -21, -14, -7) before surgery and on the day of surgery. In addition to being more convenient for patients and physicians, the amount of total drug for the weekly dosing regimen is substantially reduced.

Current Safety Issues

Thrombotic events were described in an initial uncontrolled trial of epoietin alfa therapy in patients undergoing dialysis (71). The observation of thrombotic events with epoietin alfa administration in this setting required a subsequent randomized placebo-controlled trial. Diastolic blood pressures showed a mild but significant elevation in epoietin alfa-treated patients maintained at higher levels of hemoglobin (115 g to 130 g per L) compared with lower (95 g to 110 g per L) levels or placebo-treated patients; venous access clotting was similarly increased (72). Studies of epoietin alfa therapy in the setting of uremia suggested that effects on platelet number, platelet aggregation, blood coagulation, and/or fibrinolysis could influence the risk of thrombosis during epoietin alfa therapy in patients who are uremic (73–75). The shortening of the bleeding time in these patients treated with epoietin alfa, however, is related to increased hematocrit (76,77); any thrombotic effect may, in part, be related to acute increases in hematocrit affecting blood rheology in patients at risk (78).

Subsequently, a randomized trial was conducted in hemodialysis patients with clinical evidence of congestive heart failure or ischemic heart disease to study the risks and benefits of normalizing hematocrit (to achieve and maintain a hematocrit of 42%) compared to maintenance of hematocrit at 30% (79). The primary endpoint was length of time to death or a first nonfatal myocardial infarction. The study was halted after 29 months with 183 deaths and 19 first nonfatal myocardial infarctions in the normal hematocrit cohort compared to 150 and 14, respectively, in the low hematocrit group; while the differences were not statistically significant, they were sufficient to preclude any possibility that the study would reveal a benefit for the normal hematocrit cohort. Of note, the mortality rates decreased with increasing hematocrit in both groups.

Thrombotic events have not been associated with epoietin alfa therapy in carefully controlled trials of patients scheduled for surgery. The safety of epoetin alfa therapy in patients undergoing noncardiac surgery has been demonstrated by the equal distribution of concomitant adverse events between patients treated with epoietin alfa or placebo in over 1,000 surgical patients participating in clinical trials. The overall prevalence of thrombotic events in 10 (2.8%) of 365 evaluable patients in three clinical trials (35,80,81) undergoing preoperative autologous blood donation, with or without epoietin alfa therapy, is similar to rates of thrombotic complications reported in patients undergoing orthopedic surgery. The occurrence of myocardial infarction in the setting of autologous blood donation (ABD) has also been described in patients undergoing radical prostatectomy (82). Careful studies of hemostasis, fibrinolysis, and rheology in autologous blood donors have failed to identify (pro) thrombotic changes (83,84). In view of the thrombotic events reported during the preoperative blood donation interval in both (placebo and epoietin alfa) patient cohorts, volume replacement in patients undergoing aggressive (twice weekly) phlebotomy in any patient known to have cardiovascular risks, seems prudent.

An unresolved question is the safety of epoietin alfa therapy in patients undergoing cardiac surgery and its role in this setting. In a European trial, the investigators found no differences in mortality, thrombotic events, or serious adverse events in their 76 patients between the epoietin beta-treated and placebo cohorts, nor any differences in hemostatic parameters in their patients during the 14-day preoperative interval in which increased hemotocrits (from $42 \pm 3\%$ to $48 \pm 3\%$) were demonstrated (85). In fact, the investigators in the European trial were able to demonstrate that epoietin beta-treated patients had an improved extractable oxygen perioperatively, when compared with placebo-treated patients, which was also associated with a lower incidence of lactic acidosis in the epoietin beta-treated patients (86). A U.S. study (87) also observed no differences in adverse events between epoietin alfa-treated and placebo-treated patients, and concluded that epoietin alfa therapy was well tolerated (Table 18.3). However, these findings indicated that an uneven distribution of these events between the placebo and the epoietin alfa-treated groups could not be ruled out to any degree of certainty. For example, even if the true mortality rate was 0% in the placebo group and 6% in the combined epoetin groups, the probability is only 23% (power of 0.229) that the resulting data would produce a statistically significant p value of <0.05 (88).

What is the current role of erythropoietin therapy in cardiac surgery, particularly for the U.S., in which cardiac and vascular surgeries are excluded as an indication for its use? This approach remains a valuable tool for patients with special requirements, such as Jehovah's Witness patients

TABLE 18.3
SERIOUS ADVERSE EVENTS IN TWO CLINICAL TRIALS OF CARDIAC SURGICAL PATIENTS TREATED WITH ERYTHROPOIETIN OR PLACEBO

	European Trial[a]		USA Trial[b]	
Parameter	**Placebo**	**EPO**	**Placebo**	**EPO**
Number of patients	38	38	56	126
Thrombosis or other serious adverse event	5	2	17	35
Mortality	4	4	0	7

[a]Adapted from Sowade O, Warnke H, Scigalla P, et al. Avoidance of allogeneic blood transfusions by treatment with epoietin beta (recombinant human erythropoietin) in patients undergoing open heart surgery. *Blood.* 1997;89:411–418.
[b]Adapted from D'Ambra MN, Gray RJ, Hillman R, et al. Effect of recombinant human erythropoietin on transfusion risk in coronary bypass patients. *Ann Thorac Surg.* 1997;64:1686–1693.

for whom blood transfusion is not an option (89). Until additional safety data are forthcoming, the off-label use of erythropoietin therapy in patients undergoing cardiac or vascular surgery cannot be recommended. Emerging data on the use of erythropoietin therapy in noncardiac procedures, such as elderly men undergoing radical prostatectomy (90), may provide additional evidence that perioperative elevations of hematocrit, even in patients at risk for ischemic heart disease, are well tolerated. Potential concerns that a too rapid rise in hematocrit may be harmful are not supported by experience in two clinical settings: patients receiving blood transfusions who have immediate and substantial increases in hematocrit (which is actually the desired effect) and iron-deficient patients receiving total dose iron infusions who were reported to have 2 g per dL hemoglobin increases within one week time interval, with no adverse consequences (91).

Of more recent concern is the increasing identification of patients since 1998 who have developed pure red cell aplasia (PRCA) while undergoing erythropoietin therapy (compared to a total of three cases prior to 1998) (92). This complication has been associated with the demonstration of neutralizing antibodies to erythropoietin (93,94). From 1998 through 2004, 191 cases of PRCA were reported that were antibody-mediated PRCA and where the patient was exposed to a single erythropoietic product. PRCA has been reported predominantly among dialysis patients who have taken the drug subcutaneously but not intravenously. The estimated exposure-adjusted incidence was 18 cases per 100,000 patient-years for the formulation of epoetin alfa in Eprex (Janssen-Cilag) without human serum albumin, six cases per 100,000 for Eprex formulation with serum albumin, one case per 100,000 for epoetin beta, and 0.2 cases per 100,000 for the formulation of epoetin alfa in Epogen (Amgen). These observations have led to speculation that the immunogenicity of the recombinant product was enhanced through possible combinations of changes in the manufacturing, handling, and/or administration of the recombinant product. For this reason, the route of Eprex administration in patients with chronic renal failure is now been recommended to be intravenous. Since then, the exposure-adjusted incidence has decreased by 83%.

PERIOPERATIVE EPOETIN ALFA AS AN ADJUNCT TO HEMODILUTION

Acute normovolemic hemodilution (ANH) involves removing and temporarily storing two to four units of a patient's blood just before major elective surgery in which major blood loss is anticipated. The blood that has been withdrawn is then reinfused into the patient during or after surgery. During the period of ANH, normal circulatory volume is maintained by infusing the patient with acellular fluid. Simultaneous infusions of crystalloid (3 mL crystalloids per 1 mL blood withdrawn) or colloid (1 mL hydroxyethyl starch per 1 mL blood withdrawn) have been recommended. Hemodilution is also being used in clinical trials of synthetic oxygen carriers and Hgb solutions. In such trials, blood (removed by hemodilution in an oxygen-carrying solution) greatly enhances the safety and benefit of ANH.

The rationale for the use of hemodilution is that if intraoperative blood loss is relatively constant with or without preoperative normovolemic hemodilution, then it is better to lose blood at a lower rather than at a higher level of Hct. This procedure lowers the patient's preoperative Hct to 28%. If the perioperative Hct level falls to 24%, the ANH blood units are reinfused in reverse order of their collection (i.e., last unit collected is the first unit transfused). The first unit of blood collected, and therefore the last unit reinfused, has the highest Hct, contains the most platelets, and has the highest concentration of clotting factors (95).

Clinical observations show that ANH reduces allogeneic blood use in 20% to 90% of patients with no difference in postoperative outcomes (96,97). Furthermore, ANH is substantially more cost-effective than transfusion. Total transfusion costs are significantly lower for patients who are treated with ANH, so that a unit of autologous blood obtained by hemodilution is more cost-effective than allogeneic blood preoperatively donated (95).

Hemodilution is enhanced with the effects of epoetin alfa on RBC mass. A prospective randomized trial evaluated

perioperative anemic patients undergoing radical prostatectomy with PAD (three units) compared with ANH (up to four units), with or without epoetin alfa therapy (600 IU per kg subcutaneously at 3 weeks and 2 weeks before surgery and 300 IU per kg subcutaneously on the day of surgery) (95). This study found that preoperative epoetin alfa was effective in minimizing perioperative anemia, despite hemodilution and surgical blood loss. In these patients, the mean nadir Hct levels exceeded 30% throughout surgical hospitalization. Epoetin alfa therapy in conjunction with PAD and ANH increased preoperative Hct levels and reduced the need for allogeneic blood.

SUMMARY

In recent years, the transmission of infectious diseases and other complications associated with allogeneic blood transfusion have made it a less attractive therapeutic intervention in perioperative blood loss. Attention has therefore been focused on the need to reassess current medical practices with the goal of establishing effective surgical blood management strategies that reduce the use of allogeneic blood transfusions. Erythrpoetin therapy offers a safe and effective means of reducing the need for allogeneic blood products in patients undergoing major elective surgery.

The accelerated erythropoiesis associated with epoetin alfa not only increases preoperative Hgb and RBC mass, but also accelerates depletion of serum iron stores that may contribute to the development of iron-restricted erythropoiesis. Thus, perioperative iron supplementation should be considered for iron-deficient patients and as an adjunct to erythropoetin therapy. Close monitoring of serum iron levels throughout erythropoetin therapy is also indicated, both for avoiding iron overload and for ensuring adequate levels of serum iron to meet the accelerated erythropoietic need.

Erythropoetin is a valuable therapeutic tool in surgical blood management of patients undergoing major elective surgical procedures with anticipated major blood loss, patients with a preoperative Hgb greater than 10 and no more than 13 g per dL, patients who require elective surgery, and patients with inadequate time for PAD or who are unable to participate in a PAD program due to concomitant medical conditions (e.g., cardiac disease). Finally, erythropoetin therapy has proven invaluable for patients in whom use of blood or blood products is contraindicated (89).

Future prospects for epoetin alfa in surgical blood management are based on its value in optimizing hemoglobin levels through increased erythropoiesis, as an adjunct to other emerging technologies such as artificial oxygen carriers, recombinant factor VIIa therapy, and autologous blood procurement strategies (97).

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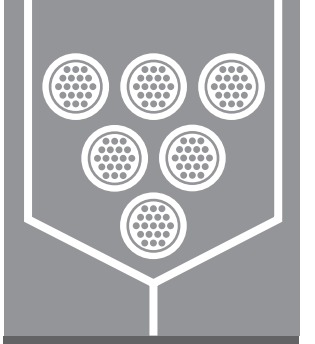

19

Hemoglobin-based Oxygen Carriers

Gregory M.T. Hare *C. David Mazer*

The evolving clinical experience demonstrating an increase in morbidity and mortality associated with allogeneic red blood cell transfusion and periodic shortages in banked blood products have sustained efforts to develop safe and effective red blood cell substitutes (1–5). In the future, red blood cell substitutes may be one of several strategies used to reduce the need for allogeneic blood transfusions (6,7). These strategies include recognition of risk factors, implementation of preoperative or intraoperative autologous donation (PAD and IAD), improvements in coagulation management, stimulation of erythropoeisis, red cell/hemoglobin salvage techniques, acceptance of lower transfusion triggers, and changes in surgical techniques. None of the strategies is mutually exclusive and current clinical practice supports their use in combination with each other.

Despite this multimodal approach to blood conservation, a significant proportion of patients who are suffering from trauma or undergoing surgical procedures require allogeneic red cell transfusions. Availability of a safe and effective blood substitute could significantly reduce the morbidity and mortality associated with such transfusions (1–4). However, the goal of developing a safe and effective substitute for red blood cells has eluded clinicians for over 100 years (8,9). The ideal red cell substitute would be universally compatible, have prolonged and simple storage capabilities, be free of contamination with infective agents, augment oxygen delivery, have a prolonged half-life, produce volume expansion, have low associated toxicity, and be reasonably priced. Early research has yielded products with unacceptable adverse effects or toxicity. However, extensive research and development have produced new compounds with improved safety and efficacy profiles. These newer generation oxygen carriers may provide clinical benefit in the near future to patients experiencing acute blood loss and reduced tissue oxygen delivery.

The two main types of red cell substitutes, or oxygen therapeutics, are hemoglobin-based oxygen carriers (HBOCs) and perfluorocarbons. Several clinical trials have demonstrated their efficacy in terms of transfusion avoidance or reduction in allogeneic transfusion in the setting of cardiac and noncardiac surgery. The role of oxygen therapeutics in other patients, including the trauma population, remains to be determined. It is possible that one or more of these oxygen therapeutics will be available for clinical use in the near future. The focus of this chapter will be to review the experimental and clinical studies assessing HBOCs. Major characteristics and stages of development of several hemoglobin-based oxygen carriers are summarized in Table 19.1. A unique proprietary chemical composition results in a distinct clinical profile for each HBOC. Several excellent reviews of the literature exist which summarize the results from experimental and clinical studies assessing different HBOCs (10–26). This chapter will review several aspects of the development of HBOCs as related to their structure, classification, physiology, toxicity, clinical use, and regulatory issues.

HISTORY

Amberson was one of the early advocates for the development of blood substitutes. He articulated the clinical need for red blood cell substitutes as early as 1936 by stating: "There is no complete substitute for blood. Yet biologists and physiologists, no less than clinicians, are so frequently confronted with situations where normal blood cannot be

TABLE 19.1
SUMMARY OF HBOCS CURRENTLY UNDER EXPERIMENTAL AND CLINICAL INVESTIGATION

Hemoglobin Classification	HBOC Modification	Commercial Products (Developer)	Hemoglobin Source	Half Life Hr	Hemoglobin Concentration g/L	COP mmHg	Viscosity Centipoise	P_{50} mmHg	Met Hb%	Mol Wt Kd	Vaso-Activity	Clinical Trials (Phase)	Reference
Tetrameric	none	none	Human	2–4	Variable	23–45	Low	8–18	<2%	64	High	None	11
Cross-linked tetramer	Diaspirin cross-linked	DCLHb HemAssist (Baxter)	Human	2–14	100	23–42	1.0	32–36	<5	64	High	Trauma (III) cardiac (III)	11,36, 150, 181–185
Surface modified tetramer	Pyridoxalated polyethylene-glycol	PHP-Hb (Apex)	Human	24–30	80	40–57	3.2	20–24	<5	>85	Low	Sepsis (II)	17,73
	Polyethylene glycol (PEG)	PEG Hb (Enzon)	Bovine	24–44	50–60	118	3.39	10–15	<5	>100	Low	Cancer (I)	17, 35, 75, 89
	Polyethylene glycol (PEG)	Hemospan (Sangart)	Human		40–80	40–49	2.5–3.2	5.5			Low	Preclinical phase I	25, 35, 100, 103, 104
Polymerized tetramer	Gluteraldehyde polymerized	HBOC 201 Hemopure (Biopure)	Bovine	9–24	130	17	1.3	36–38	<10	>150	Moderate	Cardiac (II) vascular (II) orthopedic(III)	146-149, 175, 178
		Poly-SFH-P PolyHeme (Northfield)	Human	24	100	20–25		26–30	<5	150	Moderate	Trauma (II) vascular (III)	19, 140, 170, 174, 176, 177
	o-raffinose polymerized	Hemolink (Hemosol)	Human	16–24	100	22–26	1.15	33–45	<5	>100	Moderate	Orthopedic (II) cardiac (II) Cardiac(III)	17, 141, 151, 161, 173, 180
Liposomal-encapsulated	Liposomal-encapsulated	Tetrameric Hemoglobin	Bovine	10	24–36			13–17	<20		Low	Preclinical	38
		PEG Hb	Hamster		100			9,16,30	<3		Low		87
Recombinant tetramer	α-α Cross-linked	rHb1.1 Optro (Somatogen Baxter)	Recombinant human	3–12	50	40	1.9	32–33	<5	64	Moderate	Anemia (I) surgery (II)	17, 40, 93
	Amino acid substitution	rHb2.0 (Baxter)	Recombinant human		100	62	2.3	34		64	Low	Preclinical	39, 40

obtained . . . (that) a substitute for blood has become one of the most pressing needs of the experimental laboratory" (8,p48). Due to failures with initial attempts of whole blood transfusion in the 1800s, milk from cows, goats, or humans was one of the first alternative substances utilized as a blood substitute (27). The beneficial attributes of milk transfusion were credited with "prolonging life long enough for a victim of assault to identify his assailant" (27,p22). Milk transfusion was also used to treat patients suffering from cholera in Toronto. However, due to severe systemic reactions, the practice of milk transfusion was eventually replaced by saline infusion.

Following this experience, early attempts to develop HBOCs involved the production of stroma-free unmodified hemoglobin solutions (28) prepared by simple lysis of red cells, followed by filtration of the stromal debris. These early HBOC preparations largely consisted of unmodified hemoglobin tetramers and were significantly contaminated by nonhemoglobin erythrocytic contents and membrane fragments. Upon infusion into animals and humans, unmodified hemoglobin tetramers become diluted and rapidly dissociate into two α β dimers which are excreted by the kidney (Fig. 19.1). Renal toxicity associated with these early products identified the need to modify and stabilize the structure of native tetrameric hemoglobin. This stimulated further basic research for the development of HBOCs with reduced toxicity. Structural modifications that have been utilized to minimize toxicity include: chemical cross-linking of the hemoglobin dimers to maintain a tetrameric composition; surface modification and cross-linking of hemoglobin tetramers with large molecular weight molecules; polymerization and cross-linking of tetrameric hemoglobin to produce multimeric hemoglobin molecules; liposomal encapsulation of various hemoglobin preparations; and genetic engineering of recombinant hemoglobin molecules with internal covalent cross-links (Fig. 19.1). Although none of these products has been broadly approved for clinical use, a number of phase II and III clinical trials have been completed, suggesting that one or more HBOC products may soon be available (Table 19.1). Indeed, one product has already been approved for clinical use in South Africa.

Factors that will ensure ongoing development of these products include: (a) the prevalence of transmissible blood-borne diseases; (b) the ever-diminishing pool of blood donors; (c) increasing evidence of the morbidity and mortality associated with allogeneic blood transfusion; and (d) an overall increase in the demand for surgical therapies such as coronary artery bypass grafting in which red cell transfusions are frequently required. Availability of a safe and effective HBOC would be of great value in the treatment of patients who are suffering from acute blood loss, including those experiencing trauma and those undergoing surgical procedures.

STRUCTURE AND CLASSIFICATION

The native hemoglobin tetramer contains two α and two β subunits, each of which possesses a heme prosthetic group and a globin peptide chain. The total molecular weight of

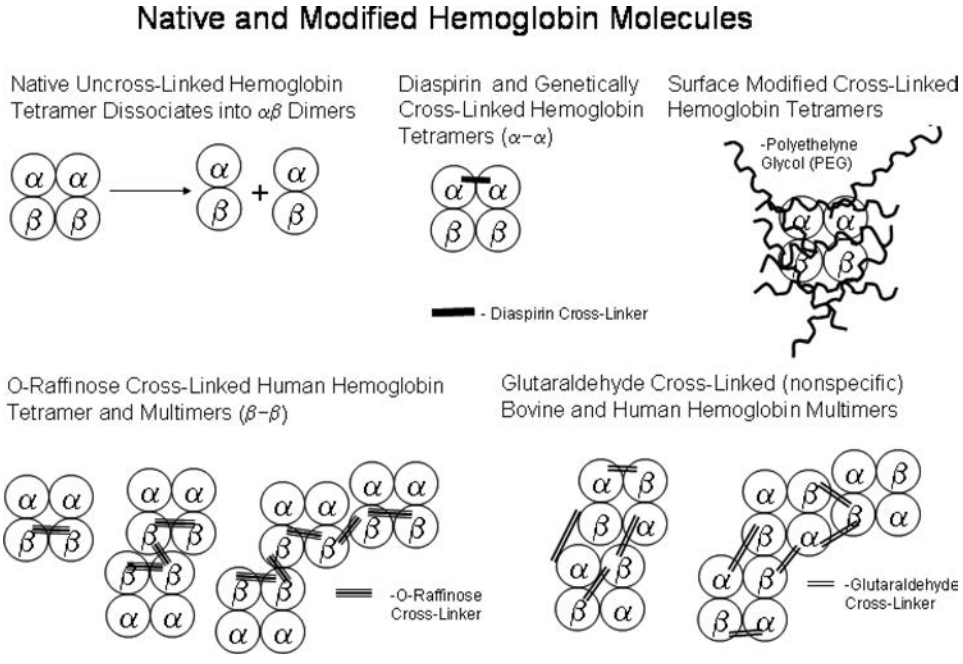

Figure 19.1 Comparison of the native hemoglobin tetramer and 4 different HBOCs. The native hemoglobin tetramer rapidly dissociates into dimers which are cleared by the kidney. Cross-linking the dimers with diaspirin leads to stability of the hemoglobin tetramer. Conjugation and cross-linking with polyethylene glycol produces hemoglobin tetramers with high molecular weight. Cross-linking with o-raffinose or glutaraldehyde stabilizes and connects hemoglobin tetramers to produce multimeric hemoglobin molecules of different molecular weights.

the hemoglobin tetramer is approximately 64 kD. Heme consists of a central iron molecule which gives blood its red color. The iron molecule is bound to four protoporphyrin molecules chemically cross-linked to form a tetrapyrole ring. Five of iron's six chemical binding sites are utilized to connect it to the protoporphyrin ring and globin molecules. The sixth iron binding site is utilized to reversibly bind a single molecule of oxygen (O_2). Under normal conditions the iron molecule is maintained in the reduced ferrous (Fe^{2+}) state in which hemoglobin can accept oxygen. In the deoxyhemoglobin conformation, the iron molecule lies slightly outside the plane of the porphyin ring and is said to be in the taut (T) state. Sequential binding of oxygen to each of the four heme groups within each hemoglobin tetramer results in a conformational change in which the iron molecule moves into the plane of the heme group. This change produces the relaxed (R) configuration of oxyhemoglobin. Sequential oxygen binding to hemoglobin occurs in a cooperative manner in which binding of each subsequent oxygen molecule increases the affinity of oxygen binding for the next heme site to be occupied. For example, the affinity of the fourth and final oxygen binding site for oxygen is increased by 20-fold by the conformational changes induced by the sequential binding of oxygen molecules to the three previous heme groups. This cooperation between the interconnected α and β subunits is responsible for the sigmoidal shape of the oxyhemoglobin dissociation curve (Fig. 19.2). Cooperative binding of oxygen, and the resulting influence on the oxygen dissociation curve, has great physiological significance; it assures nearly full oxygen saturation over a wide range ambient and alveolar oxygen tensions while simultaneously promoting the release of a large amount of oxygen to the tissues by a relatively narrow blood-to-tissue oxygen tension gradient. Moreover, several factors within the red cell are capable of modifying the oxygen affinity of hemoglobin, including intracellular pH and 2,3-diphosphoglycerate (2,3-DPG) concentration. These factors also influence the oxygen unloading capacity of hemoglobin.

Comparison of the oxygen binding capacity of red blood cells and purified free hemoglobin tetramers reveals that the free hemoglobin has a much higher affinity for oxygen than does hemoglobin within red blood cells (Table 19.2). This difference is largely attributed to the molecule 2,3-DPG, present in equal molar concentrations to hemoglobin within the red blood cell. Within a central pocket of deoxyhemoglobin in the Taut state, 2,3-DPG binds with it and forms three bonds with each of the two β globin chains. The presence of 2,3-DPG reduces the overall oxygen affinity of hemoglobin within red cells thereby increasing the amount of oxygen that can be delivered to the tissue. The value of 2,3-DPG becomes apparent in clinical conditions in which allogeneic blood is stored in blood banks. Stored red blood cells experience progressive depletion of 2,3-DPG levels which significantly increases the oxygen binding affinity. Lower 2,3-DPG levels and increased oxygen affinity reduce the ability of stored blood to deliver oxygen to tissue (29,30). This defect, referred to as *storage lesion*, is corrected in time as transfused red cells become replete with 2,3-DPG, and near normal red cell function is recovered.

The intracellular environment within the red blood cell helps to optimize the oxygen-carrying capacity of hemoglobin. For example, the red blood cell enzyme methemoglobin

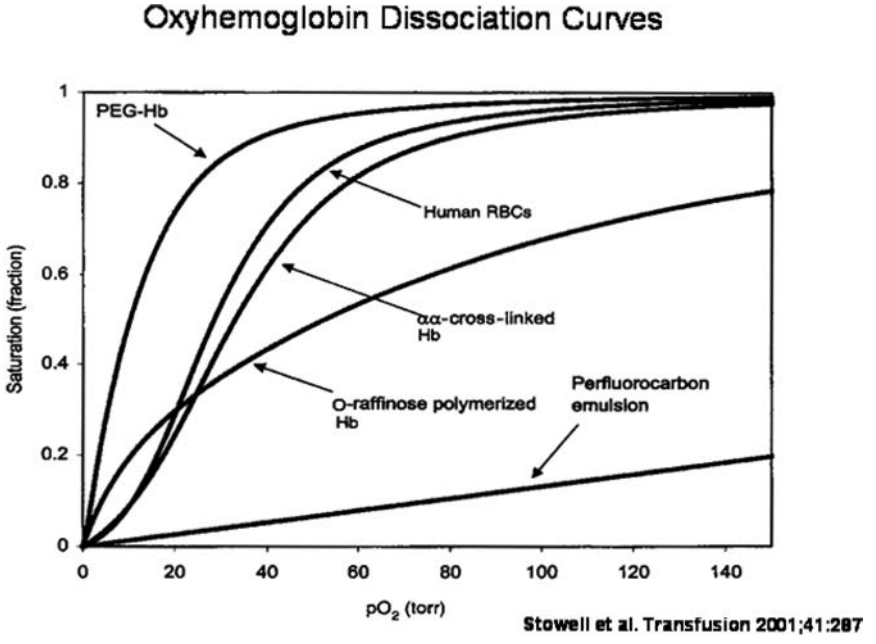

Figure 19.2 Representation of the oxyhemoglobin dissociation curve for human red blood cells (RBCs) and different blood substitutes. HBOCs with a higher oxygen affinity, such as polyethyleneglycol hemoglobin (PEG Hb), are left shifted relative to RBCs due to an increased affinity for oxygen. Other HBOCs, including diaspirin αα-cross-linked Hb and O-raffinose polymerized Hb, have reduced oxygen affinity relative to RBCs and are therefore said to be right shifted. Perfluorocarbon emulsion is an extremely right shifted oxygen therapeutic that does not contain hemoglobin (Reproduced with permission).

TABLE 19.2
COMPARISON OF NATIVE RED BLOOD CELL HEMOGLOBIN AND HBOCS

Characteristic	RBC Hemoglobin	HBOCs
Hemoglobin source	Human	Human, other animals, recombinant source
Location within blood	Inside RBC membrane	Plasma
Circulation half-life	Months	Hours to days
Oxygen affinity	Defined as normal	Higher or lower
Cooperativity of O_2 binding	Cooperative	Noncooperative
Viscosity	Blood = 2–3 centipoise (cp) Plasma = <1 cp	1.0–3.4 centipoise
Hemoglobin concentration	120–140 g/L	30–100g/L
Hemoglobin size	64 kilodaltons	64–500 kd
Nitric Oxide binding	Low (in rbc)	High

reductase, in combination with the hexose monophosphate shunt, acts to maintain the hemoglobin molecule in the reduced ferrous (Fe^{2+}) oxygen-binding state. In the absence of this enzyme, hemoglobin is oxidized to the ferric state (Fe^{3+}). Hemoglobin containing iron in this oxidation state is called methemoglobin. Methemoglobin is incapable of carrying oxygen and must be reduced to the ferrous state before oxygen binding can occur. Its presence also quantitively affects the oxygen affinity of nonoxidized hemoglobin. Increased conversion to methemoglobin occurs in patients with genetic deficiencies in methemoglobin reductase and following exposure to drugs including nitroglycerine, benzocaine, and sulfonamides (31,32). Treatment for methemoglobinemia includes administration of methylene blue which facilitates the transfer of electrons to methemoglobin reducing it to the ferrous state (Fe^{2+}).

In addition to transportation of oxygen, hemoglobin also contributes to transport other biological gases including carbon dioxide (CO_2) and nitric oxide (NO). In the tissue, CO_2 diffuses readily into red blood cells where about 10% to 20% is bound directly to the globin chains. Most of the CO_2 (70%) is hydrated to carbonic acid and then converted to hydrogen and bicarbonate by the enzyme carbonic anhydrase. The hydrogen ion becomes bound to hemoglobin, stabilizing the Taut configuration, thereby enhancing further O_2 release in the tissue (Bohr effect). Residual bicarbonate undergoes anion exchange with chloride and is carried to the lungs in the plasma. In the pulmonary microvasculature, oxygen binds to deoxyhemoglobin which then releases bound CO_2. Additionally, plasma bicarbonate is converted back into CO_2. Carbon dioxide from both sources diffuses into the alveolus and is removed by the lung ventilation. The specific physiological role of hemoglobin with respect to NO transport has not been completely defined (33,34). However, hemoglobin is a high affinity carrier of NO. This role may be accentuated when free hemoglobin or HBOCs are administered to patients. Nonencapsulated hemoglobin molecules in HBOCs bind NO with great affinity. This is one of the mechanisms by which HBOCs may promote vasoconstriction.

In aqueous solutions, unmodified tetrameric hemoglobin readily dissociates into α-β dimers. These dimers are readily filtered by the kidney resulting in a relatively short half-life (2 to 4 hours). Renal tubular toxicity associated with hemoglobin dimers precludes the use of unmodified hemoglobin tetramers in the clinical settings. Several strategies have been adopted to increase hemoglobin stability and reduce toxicity. One approach, known as intramolecular cross-linking, strengthens existing bonds, or introduces new chemical bonds, between subunits. This is achieved by utilizing reactive compounds such as diaspirin or o-raffinose. Another approach, known as intermolecular cross-linking involves linking two or more stabilized tetrameric hemoglobin units to form hemoglobin polymers with molecular weights higher than 64 Kd. Additionally, conjugation of hemoglobin oligomers with dialdehyde, o-raffinose, polyethylene glycol (PEG), hydroxyethyl starches (HES), dextrans, divinylsulphones, and acylphosphates have also been utilized. A summary of cross-linking techniques used in some HBOCs under recent experimental and clinical investigation is outlined below and in Figure 19.1 and Table 19.1.

Cross-linked Hemoglobin

Cross-linking of the hemoglobin dimers produces a stable hemoglobin tetramer with a molecular weight of 64 kD. Diacylated cross–linked hemoglobin (DCLHb) is one of the most widely studied cross-linked hemoglobins (35–37, 55,70,79,95,98,99,109). This HBOC is produced from

human hemoglobin, has delayed renal clearance, a moderate colloid oncotic pressure, relatively low viscosity, and is highly vasoactive.

Surface Modified Hemoglobin

Conjugation of hemoglobin with large molecular weight molecules such as polyethyleneglycol (PEG) or hydroxyethyl starch, results in HBOC solutions with prolonged renal clearance, high colloid oncotic pressures, high viscosity, and low vasoactivity.

Polymerized Hemoglobin

Glutaraldehyde or O-raffinose polymerization have produced several types of HBOCs which have undergone clinical trials. For these products, hemoglobin from human or bovine sources is reacted with compounds (glutaraldehyde, o-raffinose) which link adjacent molecules via amino acids within the hemoglobin molecule, and across other hemoglobin molecules. This process produces a variety of molecular weight hemoglobin polymers which exhibit reduced renal clearance, moderate colloid oncotic pressures, high viscosity, and moderate vasoactivity.

Liposome-encapsulated Hemoglobin

Liposomal encapsulation of hemoglobin molecules can provide an HBOC with high hemoglobin concentration and relatively low renal toxicity due to entrapment and clearance of liposomes in the liver and spleen (38). Encapsulation may provide the means to introduce synthetic or natural constituents designed for the protection of the hemoglobin integrity, such as methemoglobin reductase, superoxide dismutase, and catalase.

Recombinant Hemoglobin

Utilizing molecular biology techniques, it is possible to design modified hemoglobin tetramer structure and functional properties, including NO binding affinity, thereby potentially optimizing the functional characteristics of HBOCs. Modifying these functional properties may affect systemic and pulmonary vasoconstriction associated with HBOC administration (39,40).

PHYSIOLOGY OF HBOCS

Oxygen Delivery to Tissue

By definition, all HBOCs can carry oxygen. However, their ability to deliver oxygen to tissue may vary between different HBOCs in a tissue-specific manner. Factors which influence the oxygen-carrying characteristics of individual HBOCs include the type and species of hemoglobin, the cross-linking technique utilized, the molecular size of the HBOC, and the oxygen affinity. Furthermore, there are important differences between normal red cell hemoglobin and cell free hemoglobin in HBOCs (Table 19.2). Normal red cell hemoglobin is "co-operative" which means that the affinity for oxygen molecules increases as more oxygen binding sites are filled. This results in the well known sigmoidal shape of the oxyhemoglobin dissociation curve (Fig. 19.2). Most HBOCs are noncooperative and their oxygen dissociation curves are different from that of red blood cell hemoglobin. The partial pressure of oxygen at which hemoglobin is 50% saturated (P_{50}) differs greatly between human blood (28 mmHg) and different HBOCs (8 to 38 mmHg). However, because of the different oxygen-carrying characteristics of HBOCs, the absolute P_{50} value may be less important than the indication of whether the product is left or right shifted, relative to human red cell hemoglobin (Fig. 19.2). The optimal oxygen affinity for HBOCs has not yet been clearly established. To define the optimal characteristics of tissue oxygen delivery by HBOCs, a clear understanding of the physiological changes which occur in response to reduced tissue oxygen delivery must be acquired.

Mammalian physiology is particularly well adapted to compensate for significant reductions in tissue oxygen delivery secondary to hypoxemia and anemia (41–44). In both cases, a severe reduction in blood oxygen content leads to an increase in sympathetic activity (45), resulting in an increase in cardiac index (43,44,46), heart rate (44,47), and stroke volume (44). Concurrently, mean arterial blood pressure (43,44) and systemic vascular resistance are reduced (43,44,46), the available blood flow is redistributed and oxygen extraction is increased (46,47). These adaptations to optimize tissue oxygen delivery are complemented by compensatory reduction in overall metabolic requirement (42,48–51). In addition to these rapid changes, long-term adaptations, including promotion of angiogenesis and increased hemoglobin concentration, also serve to optimize tissue oxygen delivery (42,52–54). Despite these physiological adaptations, severe reduction in blood oxygen content eventually leads to inadequate tissue oxygen delivery, anerobic metabolism, and lactic acidosis (43,35,55). Such changes occur experimentally at hemoglobin concentrations near 30 to 40 g per L (43,45,56). However, clinical evidence of increased morbidity and mortality occurs in anemic patients at much higher hemoglobin concentrations near 60 to 70 g per L (1,57–63). Some experimental data suggest that anemia induced tissue hypoxia may be responsible (64,65). Therefore, strategies

which optimize tissue oxygen delivery in these patients, including development of HBOCs, may help to improve clinical outcomes.

Experiments to demonstrate the oxygen carrying effect of HBOCs have been performed in the following settings: (a) top loading experiments, in which a relatively small volume of HBOC is added to the existing circulating blood volume; (b) isovolumetric exchange or hemodilution, in which an HBOC is infused as an equal volume as blood is simultaneously removed, and (c) infusion of HBOC when the normal oxygen-carrying capacity of the blood is reduced, for example during hypoxia or following hemorrhage.

Hemodilution

Severe hemodilution represents an important condition under which the effect of HBOCs on cardiovascular physiology and tissue oxygen delivery can be studied. A number of experimental studies have demonstrated characteristic hemodynamic responses to hemodilution with HBOCs. These include an increase in MAP (66–72) secondary to increased peripheral vascular resistance and intravascular volume, (66,71–74) an increase in pulmonary artery pressure, (66,70,71,73) a variable effect on cardiac index (70–72,75,76), and improved or maintained functional capillary density (25,77). In addition, exchange transfusion with HBOCs can lead to a reduction in hemoglobin saturation (S_aO_2) (67,70) secondary to an increase in methemoglobin levels (67,70,71).

The overall effect of these hemodynamic changes can have opposing effects on different cardiovascular parameters. For example, the increase in central venous pressure, due to increased intravascular volume and vasoconstriction, would be expected to increase cardiac index. However, experimental and clinical studies demonstrate that cardiac output is often unchanged, marginally increased or marginally decreased following hemodilution with HBOCs. The tendency for all HBOCs to cause vasoconstriction, by nitric oxide binding and other mechanisms, may increase pulmonary and systemic vascular resistance enough to impede any increase in cardiac output (66–72,78,79). Despite this variable effect on cardiac index, HBOCs are still able to improve oxygen delivery to the tissue, especially to vital organs including the brain and heart.

Evidence that the brain and heart may be preferentially perfused, relative to other less vital organs, after hemodilution with HBOCs is provided by a number of experimental studies (46,47,55). In an experimental swine model, hemodilution with diaspirin cross-linked hemoglobin extended the critical hematocrit to which animals could be hemodiluted, from 6.1 to 1.2% (55). In the HBOC group, animals were hemodynamically stable without evidence of myocardial ischemia, while the control group was hypotensive with marked ST depression. Both groups demonstrated evidence of coronary vasodilation. However, coronary perfusion pressure was only maintained in the HBOC group, likely due to higher mean arterial pressure. Despite the preserved myocardial oxygen delivery in the HBOC group, evidence of skeletal muscle tissue hypoxia suggested that the heart was preferentially oxygenated (55). Similarly, cats hemodiluted to a hematocrit near 20% with an HBOC or albumin, demonstrated reductions in coronary vascular resistance and increase in coronary blood flow in response to hypoxia. These data suggest that the HBOC did not interfere with optimal coronary vasodilation (68). Despite evidence of increased myocardial oxygen delivery in the HBOC group, both control and HBOC groups demonstrated a similar decrease in skeletal muscle tissue oxygen tension. These data suggest that the heart received preferential tissue oxygen delivery with the HBOC. Anecdotal clinical evidence of improved cardiac oxygen delivery was demonstrated when a patient undergoing cardiac surgery experienced resolution of myocardial ischemia following infusion of HBOC-201 (80).

Similarly, the brain also appears to be a privileged organ which obtains increased tissue oxygen delivery with HBOCs despite evidence of significant cerebral vasoconstriction (67). Conscious rats undergoing almost complete (hematocrit 3%) exchange transfusion with a polymerized bovine hemoglobin solution demonstrated systemic hypertension, respiratory alkalosis, an overall 82% increase in CBF and a consistent increase in the cerebral glucose utilization (69). This is in contrast with studies in anesthetized animals in which hemodilution with different HBOCs was not associated with any increase in CBF (67,68,81). However, despite evidence of cerebral vasoconstriction, cerebral tissue oxygen tension and oxygen delivery were maintained or increased in anesthetized animals following extensive exchange transfusion with HBOCs (67,68,81). Further evidence of cerebral vascular constriction following hemodilution with HBOCs is provided by a study by Rebel et al. (81). They demonstrated that cerebral vessels do not undergo additional vasoconstriction in response to hyperventilation following exchange transfusion with an HBOC. This suggests that the HBOC-transfused animals are already maximally vasoconstricted. However, cerebral vessels still possess the ability to vasodilate in response to hypoventilation and hypercapnia, suggesting that vasodilatory capacity is preserved (81).

Conversely, the relative blood flow to less vital organs may be compromised following HBOC hemodilution. For example, studies which demonstrate augmented cerebral and cardiac blood flow following hemodilution with an HBOC during hypoxia exposure also demonstrate that

blood flow to the small intestine, kidney, and skeletal muscle were reduced. These data suggest that the HBOC infusion resulted in relative vasoconstriction in gut, kidney, and muscle, but not the heart or brain (68). In another study, cardiac oxygen delivery was maintained following HBOC administration while a significant reduction in skeletal muscle tissue oxygen tension was measured (55). Similarly, a 60% exchange transfusion with an HBOC resulted in a reduction in functional capillary density and tissue oxygen tension utilizing a hamster skin fold model (82). By contrast, Standl et al. (83,84) demonstrated that hemodilution with HBOC-201 resulted in a stable MAP and an increase in oxygen extraction and increased tissue oxygen tension, relative to colloid or stored blood, in dog skeletal muscle. This effect may be less pronounced with less vasoactive HBOCs (25,77). For example, renal, liver, splenic, and intestinal tissue oxygen tensions were maintained following mild hemodilution (30%) with PEG-Hb, relative to colloid hemodilution (85).

Influence of P_{50} on Tissue Oxygen Delivery

Hemodilution with HBOCs has also been utilized to determine if products with different oxygen affinities have different capacities to deliver oxygen to tissue. The P_{50} of human blood is 28 mmHg. An HBOC with a left-shifted P_{50} (P_{50} <28 mmHg) might be expected to bind oxygen more tightly and therefore have improved oxygen uptake and provide a greater oxygen reservoir. A right-shifted HBOC with lower oxygen affinity (P_{50} >28 mmHg) could be expected to have an increased capacity to unload oxygen at the tissue. In a theoretical analysis of oxygen delivery at different P_{50} values, Kavdia et al. (86) predicted that HBOCs with lower oxygen affinity (right-shifted) would increase venous partial pressure of oxygen values during normoxia and mild hypoxia, but that higher affinity HBOCs (left-shifted) would be better at maintaining venous oxygen tension during severe hypoxia. A number of experimental studies have compared the relative ability of HBOCs with different P_{50} values to deliver oxygen to tissue. Some of these studies have demonstrated that left-shifted HBOCs maintained better tissue oxygen delivery (73,87–90). Conversely, other experimental studies demonstrate that more right-shifted HBOCs were superior at delivering oxygen to tissues (91). Other investigators were unable to demonstrate any difference in oxygen delivery when comparing HBOCs with different P_{50} values (73,92,93). Overall, the existing data do not provide an adequate assessment of the optimal P_{50} values for tissue oxygen delivery. One limitation of most of these studies is that identical HBOC compounds with differing P_{50} have not been assessed (73). Therefore, the confounding effects of different HBOC structures and properties may have contributed to these different results. One study in which the same HBOC structure was modified to produce a similar HBOC with three different P_{50} values (P_{50} of 9, 16, and 30 mmHg) demonstrated that a severely left-shifted HBOC (P_{50} = 9 mmHg) had reduced oxygen delivery, while a moderately left-shifted compound (P_{50} 16 mmHg) may have exhibited more favorable oxygen delivery characteristics (87). In an additional study, resuscitation with a left-shifted HBOC (P_{50} = 8 mmHg) provided improved venular and skin tissue oxygen tension when compared to the same HBOC compound with a P_{50} of 29 mmHg (90). Further research is required to determine the optimal P_{50} for any particular HBOC solution.

Hemorrhage Resuscitation

The pathophysiology of hemorrhagic shock is much more profound than hemodilution because it involves aspects of tissue hypoxia and ischemia. The characteristic physiological responses to excessive blood loss without resuscitation include: hypotension, reduced pulmonary artery pressure, reduced cardiac output, reduced tissue blood flow, reduced capillary density, and increased oxygen extraction. These changes result in tissue hypoxia and anerobic metabolism leading to lactate production and metabolic acidosis. Untreated, the global reduction in tissue perfusion eventually leads to irreversible end-organ injury and death.

A large number of experimental studies have demonstrated that resuscitation with different HBOCs has the capacity to restore mean arterial blood pressure, (94–97) and improve tissue blood flow (98,99), capillary density (39,95,100–102), and tissue oxygen tension (96,100,101, 103–106). These positive effects reverse the base deficit (94,97,101,107), reduce anerobic metabolisms and lactate, production (89,97,108), and decrease acute mortality (89,109–111). Improved outcomes in one experimental study were attributed to an HBOC with lower vasoactive potential and a lower P_{50} value (89).

Resuscitation with HBOCs has been demonstrated to restore cerebral blood flow and cerebral tissue oxygen tension (98,106,107,112). With respect to the heart, van Iterson et al. (105) demonstrated that small volume resuscitation was better at restoring epicardial tissue oxygen tension than large volume HBOC resuscitation, possibly due to a better balance between oxygen delivery and coronary vasoconstriction. Kerger et al. (101) demonstrated that resuscitation of hemorrhaged hamsters with hemoglobin raffimer resulted in improved tissue oxygen tension and functional capillary diameter and restored base excess, relative to dextran 70 and crystalloid, in skin fold microcirculation. With respect to oxygenation of less vital organs, HBOC resuscitation restores tissue oxygen levels in kidney, muscle, liver, gut, spleen, pancreas, and skin (85,95,96, 100,101,105,106,107,113). However, these positive experimental results must be interpreted with caution because

one clinical study was stopped prematurely due to higher mortality in the HBOC group (114). Further experimental studies are required to assess the value of HBOCs in hemorrhage resuscitation before they can safely be utilized resuscitate patients from hypovolemic shock.

Sepsis

Sepsis impairs many aspects of oxygen metabolism including oxygen delivery, uptake, and utilization by cells. Severe vasodilation and systemic hypotension are characteristic of septic shock. Therefore, a therapeutic agent that restored blood pressure through vasoconstriction and improved oxygen delivery could be of value in treating these patients. HBOCs are able to deliver oxygen to tissue while promoting significant systemic vasoconstriction (67). Therefore, patients suffering from septic shock, who experience alteration in oxygen metabolism and reduced systemic vascular resistance, might benefit from HBOC administration. Theoretically, HBOCs could improve tissue oxygen delivery and reverse the distributive shock through active vasoconstriction. Indeed, a number of experimental trials have demonstrated improved hemodynamics and increased global tissue oxygen delivery and oxygen extraction in experimental models of septic shock (115–118). The increase in systemic blood pressure observed in some studies may be due to enhanced nitric oxide binding (115,116,118). However, other strategies utilizing vasoconstrictors or increased tissue oxygen delivery have not improved outcomes in patients suffering from shock. A recent Phase III clinical trial utilizing a nitric oxide synthase (NOS) inhibitor demonstrated that reduction of NO may actually be detrimental in septic shock (119). NO binding by HBOCs may produce a similar detrimental effect. Additionally, experimental studies have demonstrated that free hemoglobin may prolong and enhance the effect of endotoxin. If this effect is also observed with HBOCs, then the endotoxin mediated cell injury may be accentuated (120,121). This could have a significant impact on patients suffering from trauma or surgical interventions in whom endotoxin levels may be elevated. Therefore, potential application of HBOCs in the setting of septic shock must be approached with caution.

Ischemia

The smaller size of HBOCs relative to red blood cells may provide an advantage for perfusion through narrowed blood vessels, thereby theoretically providing improved oxygenation of ischemic tissue. In experimental models of organ ischemia, HBOCs have been demonstrated to improve tissue oxygen delivery in skeletal muscle, brain, and heart (122–124). Furthermore, postischemic reperfusion injury may also be minimized by resuscitation with an HBOC (125). However, the results from these studies should be balanced with those from a clinical trial with diaspirin cross-linked hemoglobin which demonstrated an increase in adverse events and mortality in patients suffering from acute stroke (114).

TOXICITY ASSOCIATED WITH HBOCS

When assessing the potential toxicity associated with HBOCs, caution must be exercised to assess each product independently. Physiological, pharmacological, and toxicological effects demonstrated by any given product should not necessarily be generalized to be a property of all HBOCs. No rigorous quantitative comparisons have been conducted to assess specific toxicity associated with all currently available HBOCs.

Vasoactivity

Systemic and pulmonary vasoconstriction are common adverse physiological effects associated with administration of HBOCs (126). The increase in systemic vasoconstriction has been attributed to increased activity of vasoconstricting molecules including endothelin, (126–130) and catecholamines, (131) and/or binding of vasodilatory molecules, such as nitric oxide, by HBOCs (39,132–137). The increase in vascular tone may also be a direct effect of increased oxygen delivery to tissues. In addition to direct vasoconstriction effect, the increase in blood pressure could also be due to an increase in intravascular volume secondary to increased colloid oncotic pressure. Even products with small effects on blood pressure may have significant effects on vasoactivity resulting in increased vascular resistance.

The direct vasoactive effect of different HBOCs appears to be inversely related to their molecular weight, which suggests that small molecules are more vasoconstricting (85,89,138,139). Clinical and experimental studies suggest that the order of vasoreactivity is highest for the smaller molecular weight HBOCs including diaspirin cross-linked hemoglobin, moderate for polymerized hemoglobins which contain a portion of small molecular weight hemoglobins, and lowest for surface modified hemoglobins that have higher molecular weights (25,103) (Fig. 19.3). Furthermore, recombinant hemoglobins modified to exhibit reduced nitric oxide binding have been demonstrated to restore microvascular perfusion better than hemoglobins with high nitric oxide binding (39).

The direct vasoactive capacity of HBOCs could be an advantageous or disadvantageous property depending on the clinical scenario in which it was used. For example, experimental studies have demonstrated maintenance or improved oxygen delivery to the brain following hemorrhage

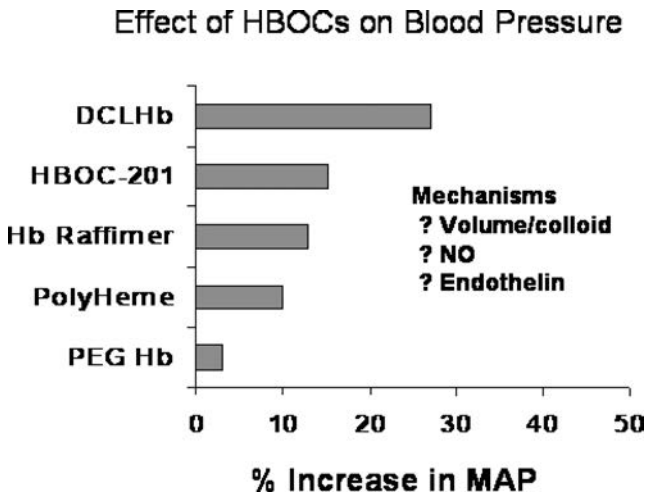

Figure 19.3 The estimated relative vasoactivity of HBOCs is in part related to the molecular weight of each product and by its chemical composition. The increase in blood pressure associated with HBOCs can be secondary to their effect on expanding intravascular volume and by direct vasoconstriction. Vasoconstriction associated with HBOCs may be secondary to nitric oxide binding or stimulation of endothelin production and release. Other vasoactive mediators may also be involved as the complete mechanism of HBOC-induced vasoconstriction has not been fully defined.

resuscitation or acute hemodilution with HBOCs (67,112). Clinical trials with significant adverse effects and increased mortality have occurred with the most vasoactive HBOCs. Therefore, the goal of reducing vasoactivity may be beneficial in subsequent generations of HBOCs.

Effects on Coagulation and Platelet Function

Infusion of liposomal-encapsulated bovine hemoglobin in rats resulted in a transient thrombocytopenia and increased radiolabelled platelet uptake in the lung and liver (140). These changes did not occur if animals underwent prior complement depletion by treating them with cobra venom factor (140). These data suggest that activation of inflammatory and coagulation pathways contributed to the sequestration of platelets following HBOC administration. Enhanced platelet deposition and restoration of hemostasis have been reported in animal models following administration of HBOCs (141,142). However, clinical studies do not identify a higher thrombosis rate in patients who have received HBOCs. In another experimental study, an HBOC had little effect on human platelet function in vitro (143). Finally, extensive hemodilution with any HBOC may lead to a dilutional coagulopathy secondary to thrombocytopenia and reduced coagulation factors.

Methemoglobin

Methemoglobin levels in human whole blood are generally kept below 1%, largely due to the activity of methemoglobin reductase within red blood cells. However, the production of HBOCs can result in the oxidation of a significant proportion of hemoglobin to methemoglobin. In all commercially produced HBOCs, the proportion of methemoglobin is generally below 10% (Table 19.1). However, if these solutions are left in oxidizing conditions in vitro, the proportion of methemoglobin increases dramatically. After administration in vivo, the methemoglobin levels remain relatively stable and at acceptable levels, possibly due to the action of red cell methemoglobin reductase and several reducing mechanisms present in plasma. Clinical reports utilizing a bovine hemoglobin glutamer in surgical patients demonstrate methemoglobin levels near or below 5% of total hemoglobin (33,34,144–146). Despite this, in some cases, a significant proportion of methemoglobin can occur. This may interfere with standard monitoring equipment such as the pulse oximeter. At methemoglobin levels near 20% total hemoglobin, the pulse oximeter readings become inaccurate, while the P_aO_2 may be normal or high. Under these conditions, a true co-oximetry measurement is required to accurately assess the actual hemoglobin saturation (31).

Organ and Tissue Toxicity

The mechanisms of potential tissue injury by HBOCs are multifactoral and may include a direct effect on enzyme systems, ischemic organ injury, oxygen free radicals, and inflammation. Evidence of elevated serum enzymes, including aspartate aminotransferase (AST), lipase, and amylase, occurs by an unknown mechanism, but could possibly be related to a direct effect on these enzyme systems (147–149). In addition, HBOCs may cause tissue injury by acting as a source of free radicals. Oxidative stress could occur due to the direct effect of hemoglobin as a source of oxygen free radicals or an indirect effect on the normal antioxidant protective mechanisms such as nitric oxide (150–154). In addition, experimental studies in vitro have suggested that proinflammatory properties of hemoglobin result in increased cytokine levels, possibly mediating inflammatory tissue injury (155,156). Tissue ischemia due to profound vasoconstriction may also result in organ injury secondary to NO scavenging and activation of endothelin mediated mechanisms.

Cardiac Function

HBOCs do not appear to directly affect cardiac contractility. The overall net effects on acute cardiac function depend upon the balance of effects on improved myocardial oxygen supply and increased myocardial oxygen demand secondary to systemic vasoconstriction. Many experimental and clinical studies demonstrate either unchanged or decreased cardiac output following exchange transfusion with HBOCs (70–72,75,76). Standl et al. (123,157) have

demonstrated improved myocardial and skeletal muscle oxygen tension when an HBOC was administered in experimental models of coronary and skeletal muscle ischemia. However, in some species-specific animal models (monkeys and pigs), infusion of HBOCs resulted in the development of small areas of multifocal myocardial necrosis, in the papillary muscle, septum, and right ventricle (158). In these studies, the presence of microscopic lesions was not associated with a detectable decline in myocardial function or release of biomarkers. A number of clinical trials have been performed utilizing HBOCs in cardiac surgical patients (145,148,159). One of these trials was stopped prior to target enrollment because of a higher incidence of adverse cardiac events. Continued surveillance of cardiac toxicity will be required in the assessment of next generation HBOCs.

Cerebral Injury

Under normal conditions, the cerebral neurons are protected from potential toxic effects of hemoglobin by two barriers: the red cell membrane and the blood brain barrier. Although pressure-related filtration of diaspirin cross-linked hemoglobin has been described, it is unknown whether filtration of other HBOCs occurs across the intact cerebral microvasculature (162). HBOCs could be protective to the brain if they increased cerebral oxygen delivery to hypoxic/ischemic areas or if they decreased NO mediated neurotoxicity (67,161). Exposure of neurons to unmodified hemoglobin has been demonstrated to increase neuronal injury in vitro (162). However, one experimental study was not able to demonstrate a direct toxic effect of an HBOC on cultured neurons, which suggests a reduction in direct toxicity (167). Despite this report, the potential for neuronal toxicity is highlighted by an increased mortality in stroke patients treated with a cross-linked hemoglobin tetramer (114). Although the potential mechanisms of neuronal injury have not been defined, increased vascular permeability due to HBOC administration may accentuate cerebral edema and be detrimental in patients suffering from neurological injury (164,165). Thus, the effect of different HBOCs in clinical situations with blood brain barrier injury remains to be determined.

Hepatic and Gastrointestinal Function

Administration of HBOCs has been demonstrated to cause histological evidence of liver injury (166) and elevation of certain hepatic and pancreatic enzymes (146,149–151). Serum bilirubin increases in a dose-dependent manner, presumably as a result of breakdown of the HBOC hemoglobin. The presence of both conjugated and nonconjugated bilirubin suggests that this is due to the expected metabolism of the porphyrin by the reticuloendothelial system (144). These changes result in a certain number of patients presenting with clinical jaundice (159). Clinical and experimental studies have demonstrated that administration of HBOCs causes elevation of serum amylase and lipase, of greater frequency and/or magnitude of elevation than in the appropriate control subjects undergoing the same procedures. These elevations may not be diagnostic of pancreatitis since they are transient and are only rarely associated with clinical signs and symptoms of pancreatitis. The interpretation of these values may also be confounded by other variables including the coadministration of hydroxyethyl starch, which can also cause elevated amylase levels.

Increased lactate dehydrogenase (LDH), creatine kinase (CK), aspartate aminotransferase (AST), and lactate have also been reported in humans receiving HBOCs (144, 147–149). The mechanism of these increases has not been defined, however, they may result from a direct effect of HBOCs on these enzyme systems or an indirect oxidant effect (150–154). More specific markers of hepatocellular injury (gamma glutamyl transferase-GGT, alanine aminotransferase-ALT) do not seem to be affected to the same degree (149).

Awake patients who receive HBOCs can develop symptoms of abdominal pain, dysphagia, nausea, and vomiting (149). These symptoms are thought to be related to nitric oxide scavenging in the gastrointestinal system, possibly leading to decreased gut perfusion and/or failure of NO-mediated relaxation of sphincters. The incidence of these symptoms may be reduced in patients who receive HBOCs under general anesthesia, however such symptoms are still recorded postoperatively and appear to correlate with the dose of HBOC administered (159). In animals, administration of HBOCs has been associated with changes in structure of microvilli suggesting the possibility that gut dysfunction may lead to translocation of bacteria across the intestinal wall (165). The magnitude of the observed changes after treatment with two different HBOCs was not identical, indicating that the effects may be product-specific rather than a class effect. Evidence of gut hyperoxia following hemorrhage and HBOC resuscitation suggests that oxygen-free radicals may contribute to gut injury (105).

Renal Injury

Unmodified hemoglobin tetramers are known to degrade into $\alpha\beta$ dimers which are filtered by the kidney and produce renal toxicity through a direct effect on renal tubules. However, structurally modified HBOCs currently utilized in clinical trials have not provided significant evidence of renal toxicity (144,147,167). Furthermore, one experimental study which demonstrated histological evidence of hepatic injury following HBOC administration, did not show evidence of renal injury (166).

Antibodies

Patients who receive HBOCs could develop antibodies to the modified hemoglobin molecule. This immunoreactivity

could be secondary to preexisting antibodies or newly formed antibodies to a novel antigenic stimulation. The stress response to surgery may also influence antibody production. However, there appears to be little evidence of development of associated autoimmune phenomenon associated with such antibody production and the clinical relevance is questionable.

Interference with Laboratory Tests and Clinical Monitors

HBOCs are known to interfere with several laboratory tests. The cell-free hemoglobin causes a dose-dependent increase in serum hemoglobin levels which may be misinterpreted as evidence of hemolysis. This may be of particular importance when cross-matching patients for subsequent allogeneic blood transfusions as free hemoglobin may be interpreted as evidence of an incompatible cross-match. Measurement of hemoglobin concentration and oxygen saturation by co-oximetry should be accurate but the hematocrit will no longer correlate with total hemoglobin concentration following HBOC administration. The hematocrit will only be indicative of red blood cell hemoglobin. Many laboratory tests utilize a colorimetric assay technique. These tests may be affected by the presence of free hemoglobin. Assays that may be affected include liver function tests, cardiac and pancreatic enzymes, albumin and total protein determinations, and fibrinogen. Corrective algorithms may be able to reduce these errors, but utilization of assays or devices that are not affected by such interference would be more favorable.

CLINICAL TRIALS UTILIZING HBOCS

An extensive number of potential clinical uses for HBOCs exists. These can be grouped as follows: (a) as a bridge to transfusion or transfusion alternative when blood is not available due to logistic difficulty (cross-match delay) or limited supply; (b) as the initial resuscitation fluid following trauma, gastrointestinal bleeding, cardiac arrest resuscitation, and cerebral anoxia; (c) treatment of ischemia-limited oxygen delivery such as stroke and myocardial ischemia; (d) Increased oxygen delivery to hypoxic/ischemic tumors to optimize chemotherapeutic or radiation therapy; and (e) blood doping to improve cardiovascular function (168,169).

There is a rapidly growing body of literature on HBOC administration to humans. These reports consist of case reports; Phase I trials that involve administration of HBOC to normal volunteers; Phase II trials that involve small safety studies in a patient population of interest and have efficacy as a secondary outcome; and Phase III trials that involve large efficacy studies with safety as a secondary outcome. There are also several case reports of compassionate release and administration of HBOCs in the setting of acute blood loss, hemolytic anemia, and sickle cell crisis. The clinical benefit of HBOC administration include the reversal of clinical signs of decreased tissue oxygen delivery (170–172). At the time of writing of this chapter, the authors are unaware of any product that is currently available for compassionate use.

The primary efficacy outcome in most clinical trials with HBOCs is avoidance and/or reduction of allogeneic blood transfusion. There are two types of studies done using red blood cell substitutes in the surgical setting. In the first type of study, randomization does not occur until the time of first transfusion decision (prn transfusion), after which either study product or allogeneic red blood cells are administered according to the study protocol. Thus, all control patients receive allogeneic red blood cells. In this type of study, HBOC administration is reactive to a predetermined transfusion trigger. Noncardiac surgical studies generally conform to this type of study. The second type of study usually involves cardiac surgery patients. In these studies, the investigational product, or a control colloid solution, is given in combination with acute normovolemic hemodilution (ANH) or intraoperative autologous donation (IAD). In these cases, it is expected that HBOC administration will increase the amount of autologous blood harvested for subsequent reinfusion postoperatively. In this type of study, HBOCs are administered proactively, in an attempt to prevent allogeneic blood transfusion and not all control patients are transfused with allogeneic blood.

A number of HBOCs have been involved in clinical trials, as summarized in Table 19.1.

PolyHeme

PolyHeme (Poly SFH-P, glutaraldehyde cross-linked pyridoxalated human hemoglobin, Northfield Laboratories Inc., Chicago, IL.) is an HBOC made from human hemoglobin. Gould et al. (173) reported a small (n = 44) randomized trial using PolyHeme in acute trauma and emergency surgery. After infusion of up to six units of HBOC, Polyhemeaccounted for about 40% of total circulating hemoglobin and reduced the total number of allogeneic transfusions. The incidence of mortality was 2/21 in the treated group and 0/23 in the control group. A more recent report documented the rapid administration of 1 to 20 units of PolyHeme to 171 trauma or surgical patients (174). The average total hemoglobin concentration was maintained greater than 65 g per L despite nadir red blood cell hemoglobin concentrations of less than 30 g per L in 40 patients. When compared to historical controls (treated years earlier), patients treated with PolyHeme maintained a red blood cell hemoglobin concentration less than 53 g per L and had a lower 30-day mortality rate.

HBOC-201

Hemoglobin glutamer-250 (HBOC-201, Hemopure, Biopure Corp) is a 13% solution of bovine glutaraldehyde polymerized hemoglobin in a balanced electrolyte solution. A small dose escalation trial concluded that this HBOC was well tolerated in doses up to 2.5 g per kg body weight (144). At these doses, a delayed dose-dependent increases in plasma methemoglobin was observed. Furthermore, a small number of patients had transient increase in transaminases and skin discoloration, and one patient had mast cell degranulation with hypotension. Kasper et al. (146,175) studied the hemodynamic and oxygen transport effects of HBOC-201 in patients undergoing hemodilution prior to elective abdominal aortic surgery. In these studies, HBOC-201 administration was associated with a significant increase in blood pressure, systemic vascular resistance, and oxygen-carrying capacity, and a decrease in cardiac output and overall oxygen delivery. In addition to these studies, a randomized trial of HBOC-201 in cardiac surgery has also been completed (145). Ninety-eight patients were randomized to receive either HBOC-201 or allogeneic red blood cells for the first three transfusion decisions. Thirty four percent of the HBOC-201 patients avoided allogeneic transfusion. None of the control patients avoided an allogeneic transfusion. Additionally, the average number of units of allogeneic red blood cells transfused was reduced from 2.2 to 1.7 units in the HBOC group ($p = 0.05$). Oxygen delivery was similar, but oxygen extraction was higher in the patients who received HBOC-201.

HBOC-201 has also been studied in patients undergoing aortic surgery. LaMuraglia et al. (147) randomized 72 patients undergoing elective infrarenal aortic operations to receive either HBOC-201 or allogeneic RBCs at the time of first transfusion decision. Transfusion decisions were made by clinical criteria rather than by the use of strict protocols. Patients received a maximum of four doses (150 grams) of HBOC-201 or four units of red blood cells. Twenty-seven percent in the HBOC-201 group avoided allogeneic red blood cell use. This was significantly different from the control group in which all patients received allogeneic blood as specified by the study design (0% transfusion avoidance). However, there was no significant difference in median number of allogeneic red blood cell units given (HBOC-201 2.0 versus RBC 2.5). Mean arterial blood pressure rose significantly after infusion in the HBOC-201 group but not in the RBC group. The increase in serum urea nitrogen was significantly higher in the HBOC-201 group. Similarly, the creatinine, lipase, and AST increases tended to be greater in the treated group. In addition, more rashes were reported, possibly related to the deposition of the HBOC-201 in the skin.

Hemolink

Hemolink (Hemoglobin raffimer, Hemosol Corp, Mississauga, Ontario) is an oxidized-raffinose cross-linked and polymerized human hemoglobin prepared in 10% solution of Ringer's lactate. In a Phase I study, it produced no significant effect on renal or liver function, although as expected from the hemoglobin load, there was a dose-dependent rise in unconjugated bilirubin (149). Consistent with a possible nitric oxide binding effect, there was a dose-dependent rise in mean arterial blood pressure and abdominal discomfort in some patients. The authors concluded that Hemolink was a safe and effective hemoglobin-based oxygen carrier.

Hemoglobin raffimer has been subsequently evaluated in conjunction with intraoperative autologous donation in phase II and III studies of coronary artery bypass surgery. In the first study, 60 patients undergoing elective primary coronary artery bypass grafting with cardiopulmonary bypass were enrolled in four dose escalating blocks (250 to 1000 cc) of either hemoglobin raffimer or pentastarch. Hemoglobin raffimer administration produced significantly higher hemoglobin concentration. Fewer patients in the hemoglobin raffimer group required perioperative transfusion compared with control patients ($p = 0.003$ to 0.05). The most frequently reported adverse events were increased blood pressure, nausea, and atrial fibrillation, and all serious adverse events were felt to be unrelated or unlikely related to study drug (161). A Phase III multicenter, blinded, randomized trial evaluating 750 mL of hemoglobin raffimer in combination with IAD in CABG surgery has also been completed (177). Hemoglobin raffimer treated patients had a higher hemoglobin concentration and lower allogeneic transfusion rate than patients given pentastarch. The total number of units of allogeneic blood given to treated patients was less than that in controls. As expected, hemoglobin raffimer patients had higher serum bilirubin and higher blood pressure. Another Phase III clinical trial with hemoglobin raffimer in patients undergoing CABG surgery was recently terminated prematurely due to an imbalance in cardiac events reflective of myocardial infarction. The data has yet to be reported, so the role of hemoglobin raffimer, or possible mechanisms for this imbalance, are not clear. The efficacy endpoint was not met in this study, possibly due to the early termination of the study.

DCLHb

Diaspirin cross-linked hemoglobin (HemAssist, DCLHb, Baxter Healthcare, Boulder, Co) is another HBOC made from human hemoglobin cross-linked at the α99 lysine residues. It has a P_{50} of 32 mmHg and a half-life of

approximately 2 to 11 hours. DCLHb has been investigated in a variety of clinical settings including trauma, major noncardiac surgery, and cardiac surgery (178–180). In the cardiac surgery trial, 209 patients were randomized to receive up to three 250 mL infusions of DCLHb or three units of packed red blood cells when transfusion was indicated (150). Allogeneic transfusion until postoperative day 7, or hospital discharge, was avoided in 19% of DCLHb patients compared to 0% of control patients ($p < 0.05$). However, there was no difference in the average total number of allogeneic red blood cell units (2.7 units) given to either group. DCLHb administration was associated with a significant elevation in systemic and pulmonary blood pressure and systemic and pulmonary vascular resistance. In addition, total bilirubin, amylase, lipase, urea, creatinine, and total CK were all significantly elevated 24 hours after DCLHb. Mortality was not different between groups, but the DCLHb group had more serious and nonserious adverse events reported.

However, not all clinical trials with HBOCs have yielded positive results. The DCLHb Traumatic Hemorrhagic Shock Study Group conducted a Phase III study in which 112 patients with hemorrhagic shock and unstable vital signs were randomized to receive 500 to 1000 mL of diaspirin cross-linked hemoglobin or normal saline during the initial hospital resuscitation (181). The study was terminated early because of a significantly higher mortality in the DCLHb group at 48 hours (38% versus 15%, $p = 0.01$), and at 28 days (46% versus 17%, $p = 0.03$). Other outcomes included morbidity as measured by MOD/time curve (DCLHb 348 versus control 202, $p = 0.03$) and lactate levels at 24 hours (DCLHb 2.9 versus control 2.6, $p = 0.29$). The mortality rate in the treated group was higher independent of demographic and physiological variables which included age, sex, type of injury, hemoglobin level, blood pressure, heart rate, base deficit, and trauma injury score. Possible explanations for the unexpected higher mortality rate include a difference in clinical status, as evidenced by higher preinfusion cardiac arrest rates, lower preinfusion systolic and diastolic blood pressures, higher TRISS predicted mortality rates, higher incidence of penetrating trauma, and a higher number of patients with severe head injury. In addition, the vasoconstrictive effect of DCLHb may have accelerated bleeding and/or led to reduced tissue perfusion despite equivalent perfusion pressures (37). Another trial in major noncardiac surgery with DCLHb was also terminated early because of safety concerns. Patients in the treatment group had a higher incidence of jaundice, urinary side effects, and pancreatitis (182). The development of this product has been terminated by the manufacturer.

REGULATORY ISSUES

As of 2004, none of the HBOCs under development has been approved for clinical use in North America. Current HBOCs under assessment include:

1. HBOC-201, Hemopure (Biopure Corp, Cambridge, Mass): This product has been approved for clinical use in South Africa and data has been submitted to the FDA. However, further preclinical data is required. A related product is approved in the U.S. for veterinary use for the treatment of canine anemia.
2. Poly SFH-P, PolyHeme (Northfield Laboratories Inc., Chicago, Ill.): This product is under assessment in a clinical trial that has enrolled approximately half of the target population in a prehospital resuscitation (ambulance).
3. Hemospan (Sangart Inc, San Diego, Calif): Phase I trials have been completed. Phase II trials are currently underway in Europe.
4. Hemolink (Hemoglobin raffimer, Hemosol Corp, Mississauga, Ontario): This company has put their clinical program on hold to evaluate adverse cardiac events in the most recent phase II/III CABG study. The company is performing preclinical studies on other modified compounds.
5. DCLHb, (HemAssist, rbHb Baxter Healthcare, Boulder, Co): This company terminated their hemoglobin therapeutics program in September 2003.

Prior to receiving regulatory approval, HBOCs must undergo significant preclinical and clinical assessment. New products must be carefully and completely characterized and animal models must emulate the clinical setting of intended use. The potential for inherent toxicity must be evaluated extensively. The safety profile of stored allogeneic red blood cells must be evaluated and compared to the relative toxicity and adverse outcomes experienced with HBOCs. Currently, the regulatory requirements for the use of HBOCs are under review. The Centre for Biologics Evaluation and Research (CBER) of the FDA is currently preparing a guidance document entitled "Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutic as Red Blood Cell Substitutes." Copies are available for comment and can be obtained directly from the FDA or via the Internet on their Web site at http://www.fda.gov/cber/guidelines.htm. These nonbinding guidelines are intended to provide recommendations for the current development of oxygen therapeutics and for the issues to be considered when evaluating regulatory submissions related to oxygen therapeutics. The safety issues listed in the draft document that require consideration include removal of all nonmodified tetrameric hemoglobin molecules, vasoactivity, cardiac

toxicity, gastrointestinal symptoms, bacterial translocation, proinflammatory and procoagulant potential, oxidative stress, pancreatic and liver enzyme elevation, laboratory interference, endotoxin synergy, and neurotoxicity.

Previous efficacy endpoints in clinical trials have included avoidance and reduction of allogeneic transfusion. From the regulatory viewpoint in the guidelines document, the potential clinical uses for oxygen therapeutics include perioperative and trauma indications, local effects (such as enhancement of tumor radiosensitivity), and/or improvement of regional perfusion. In terms of efficacy, the endpoints should be either direct or surrogate measures of clinical benefit that are translatable to improved survival and substantial avoidance of red blood cell transfusions without offsetting adverse outcomes. Given the potential for off-label use, the guidance document recommends that products should be studied in a variety of clinical settings.

CONCLUSION

The search for a substitute for the oxygen-carrying characteristics of red blood cells is almost as long as the history of transfusion. Hemoglobin-based oxygen carriers are an interesting group of compounds which can augment tissue oxygen delivery and may decrease red blood cell transfusions. Each product has its own limitations and advantages. Large amounts of preclinical and clinical research have demonstrated potential target populations, beneficial properties, adverse effects, and a direction for future study by both academic and regulatory agencies. It is hoped that a safe and efficacious HBOC will be available for clinical use in the near future.

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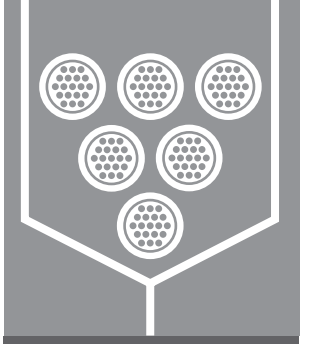

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Perfluorocarbon Emulsions: Artificial Gas Transport Media

Bruce D. Spiess

Perfluorocarbon (PFC) emulsions are one of two main technologies in development to function as oxygen therapeutics. Hemoglobin preparations and PFC emulsions are sometimes referred to as *artificial blood* or *blood substitutes.* Neither one is a true blood substitute or artificial blood. At best, they represent pharmacological approaches to intravenous gas transport. Blood functions in coagulation, inflammation, protein transport, humoral transport, and a multitude of other functions. Both PFCs and hemoglobin preparations will only partially fulfill the one function of moving respiratory gases through the circulation. There has long been a wish for a stable, nontoxic, effective intravenous solution that could be stored for long periods of time on a shelf, rapidly prepared, or simply infused and immediately function in the transport of oxygen. Such preparations need to be robust and able to withstand a wide temperature stress during storage and shipment. At best, these agents may be able to partially fulfill this role. However, they will have an entirely different pharmacological and physiological profile from human blood. Therefore, the conception that a health care worker will simply turn to these instead of a unit of packed red cells is a misuse of present knowledge. There, however, may be future indications for these gas transport solutions instead of human blood transfusion. This chapter discusses the state of the science as it exists today in PFC emulsions.

One, Fluosol DA 20%, was approved by the U.S. Food and Drug Administration (FDA) for use in coronary angioplasty. It is not presently manufactured but we should learn from its experience how that agent went through the FDA. Some other third-generation formulations are presently undergoing FDA testing. Almost certainly in 5 to 10 years, this chapter will be outdated as indications, contraindications, and perhaps formulations not now even conceived of will come to the forefront.

HISTORY

Carbon fluoride chemistry was a product of World War II and was extremely active in the 1950s. Early observations that liquid, fully fluoridated hydrocarbons could dissolve oxygen were important. The carbon fluoride bond is stable and high energy (504 kJ per mol) (1). To understand the effect of fluoridating hydrocarbons, one can examine what happens with a simple benzene ring (2). When one fluorine molecule is added to each carbon atom of the ring, hexafluorobenzene is created. Hexafluorobenzene is interesting in that it has potent anesthetic properties but is also quite toxic; losing its fluourides, it causes both renal and hepatotoxicity. It demonstrates almost no increase in respiratory gas solubilities. Hexafluorobenzene if then fully fluoridated becomes perfluorocyclohexane, and that molecule has no anesthetic properties. It can, however, dissolve twice the oxygen carried by benzene.

In 1966, Clark and Gollan (3) produced a fury of scientific and lay interest when they published photographs of mice and rats immersed in liquid PFC breathing oxygenated pure PFC liquid. Speculation of liquid breathing as a method for undersea exploration and for submarine escape was widespread. Other researchers thought that if the compounds were effective enough to transport oxygen to lungs,

then they could be useful as intravenous oxygen transporters (4,5). The idea of liquid fluorocarbon breathing made it all the way to Hollywood with the movie "The Abyss," which showed deep divers using the technique to explore the deep oceans. Perfusion of various isolated organs was demonstrated, and, indeed, mammal brain could be maintained electrically active with a warm PFC containing perfusate alone (5). PFC kept cellular activity going for the same time period as a red cell-based perfusate. Isolated rat hearts were kept beating with either a perfluorobutyltetrahydrofuran (FX80) solution or red cell perfusion (4).

Infusion of these early PFC solutions into intact animals caused gaseous microemboli and macroemboli, leading to disastrous pulmonary complications (6). Native PFC (an oil) is immiscible with water. Plasma and pure PFC separate, much like olive oil and vinegar in salad dressing. However, if the mixture was sonicated before infusion, these complications could be decreased and partial transfusions of amphibians and total exchange transfusion of rats were possible (6–8).

One problem leading to gas embolism was not only the lack of ability of the PFC to mix with plasma, but also the vapor pressure of the individual hydrocarbon chains selected for use. Multiple different carbon skeletons were tested and fluoridated (9). Those with low vapor pressures will create intravascular gas bubbles at normal body temperatures (2,6). However those with high vapor pressures have long tissue and whole body dwell times.

Clark (2) recognized these problems and made some early attempts to create an emulsion using the industrial surfactant Pluronic F68. A combination of perfluorodecalin and perfluorotributylamine was created (FC-43), which was stable and was used to replace red cells in a number of animal species (2,7,9,10). It was tried in Japan in 1978 as a treatment for human anemia. Although initial results from Japan were encouraging, the trials in the United States could not support its usefulness (11–13). FC-43 appeared to have a long half-life (years) because perfluorotributylamine has a high vapor pressure. Another formulation, Fluosol DA 20% (Green Cross Corporation of Osaka, Japan) used perfluorodecalin and perfluorotripropalamine with pluronic F68 and egg yolk phospholipids (10,14). This preparation underwent considerable testing in animals and humans. In the United States, it did garner FDA approval for use not as a blood substitute but as a perfusion solution for coronary artery angioplasty catheters. Its use remained inconsequential because of the way it is supplied and the steps required for its preparation. Fluosol was supplied in frozen form requiring it to be thawed, mixed with emulsifiers, and then sonicated before infusion. Also, before infusion in angioplasty, it needed to be oxygenated. These steps were time-consuming and cumbersome in an active cardiac catheterization laboratory. It was withdrawn from the market due to lack of utilization.

The early preparations of PFC contained only 10% by volume of active PFC and 90% water, electrolyte, and emulsifying agents (10). Although most PFC compounds can carry 40 to 60 vol% of oxygen at 1 atmosphere (760 Torr), with the emulsions being only 10% PFC, the oxygen-carrying capacity was already limited. That limitation has led to the development of second-generation compounds that are now 40% to 80% by volume PFC (15,16). These second-generation and third-generation emulsions use emulsifiers other than pluronic F68 and therefore may have fewer systemic side effects. At the present time, the third generation compounds are undergoing FDA testing.

CHEMISTRY AND GAS-CARRYING CAPABILITIES

PFCs possess a unique ability for enhanced gas solubility. This is to be distinguished from oxygen molecular binding with hemoglobin. All nonpolar gases, including oxygen, nitrogen, and carbon dioxide, are solubilized within the liquid PFC. One way to conceive of this is that gas molecules are dissolved between PFC molecules. The concentration of any given gas within the PFC is dependent only on Henry's law and is therefore proportional to the partial pressure of a particular gas. One gas does not interfere with the transport potential for another gas. Therefore, if a patient is breathing a high oxygen content but has dissolved nitrogen within tissue, that nitrogen will be soluble within the PFC dependent only on the innate solubility and the partial pressure of each gas independently. Each gas is freely movable to another adjacent solution or tissue, again based only on partial pressure gradients. Therefore, oxygen carried in PFC is completely available for metabolic processes (Fig. 20.1). Because gas-carrying capacity is dependent only on Henry's law, a straight-line dissociation curve for oxygen is created with PFC.

The gas dissociation curve of PFC contrasts sharply with the sinusoidal curve of hemoglobin oxygen dissociation. Oxygen is carried by hemoglobin chemically bound to its various heme moieties. Occupation of each of the four heme moieties in turn changes the stability of oxygen binding to the next one. A wide range of physiological conditions affect the oxyhemoglobin dissociation curve, including temperature, 2,3-diphosphoglycerate (2,3-DPG) concentration, and pH. PFC is completely unaffected by enzyme degradation, and pH changes have no effect on the gas solubilities. Furthermore, 2,3-DPG has no effect on oxygen release from PFC. Temperature does not cause the same effects as it does in hemoglobin oxygen binding. Hypothermia actually increases oxygen, nitrogen, and

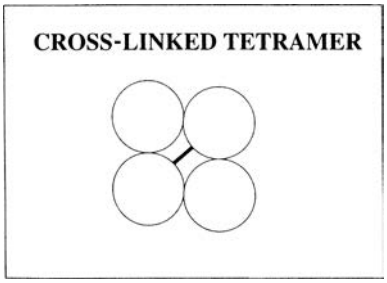

Figure 20.1 Oxygen content of whole blood at two different hemoglobin concentrations. Note the sinusoidal curve of the oxyhemoglobin dissociation curve. Changes in pH, body temperature, and 2,3-diphosphoglycerate shift the curves to the right or left. Note that the three PFC lines are not sinusoidal in relation to PO_2. Rather, a straight-line relationship exists between perfluorocarbon concentration and dissolved oxygen. In 100% pure PFC, as much as 40-60 vol% of oxygen can be carried. However, in stable emulsions administered intravenously, the total oxygen-carrying capacity is approximately 1 vol% for first-generation (Fluosol DA-20%) compounds and 4-8% for second-generation (40% v/v) emulsions. All dissolved oxygen in PFC is metabolically available.

carbon dioxide solubility in PFC just as hypothermia increases gas solubility in plasma.

Physiologically, the PFC gas transport therefore becomes quite unique. It is dependent on the partial pressure of a gas (oxygen or nitrogen) and the available concentration of PFC within the bloodstream. As noted before, PFCs are organic compounds substituted with fluorides and therefore are quite immiscible with water. Stable emulsions must be formed using some sort of emulsifying agent. First-generation and second-generation PFC emulsions have created particles of 0.01 to 0.3 μm (17–19). These are considerably smaller than erythrocytes and therefore come close to acting as part of the plasma phase of the blood. Oxygen is very insoluble in plasma, and therefore the plasma acts as a barrier that oxygen must transit from erythrocytes to the tissues. PFC emulsions increase oxygen diffusion by as much as 17-fold to 50-fold when added to plasma (20). A great deal is still unknown about what can change oxygen delivery characteristics from red cells. The small particle size of the emulsions leads to a massive increase in surface area available from gas exchange. Once again, it is unclear how much this factor can assist in oxygen transport.

Hemoglobin can be affected by other factors than the oxyhemoglobin dissociation curve and also it may have a number of roles that clearly PFC does not possess. Hemoglobin has a buffering capacity as it binds carbon dioxide. A number of compounds can cause the formation of reduced hemoglobin or methoxyhemoglobin that cannot take part in oxygen transport at all. These compounds have no effect on the oxygen transport of PFC. Carbon monoxide irreversibly binds to hemoglobin, thereby occupying sites that could chemically bind and release oxygen. PFC is unaffected by carbon monoxide; however, PFC would carry it in equilibrium with the partial pressure. Hemoglobin is a profound nitric oxide binder (21–23). Free hemoglobin and some of the new polymerized hemoglobin compounds being investigated as blood substitutes create differing elements of hypertension on infusion because of the preferential flow of nitric oxide to these molecules and away from their physiological target organ, the vascular smooth muscle. There is no suggestion today that PFC would have any role in nitric oxide flow other than that dictated by Henry's law. Also there is no suggestion that PFC would change the carbon dioxide movement other than to have it in equilibrium with the partial pressure of the surrounding tissues. In underperfused areas PFC could increase carbon dioxide clearance if red cells cannot penetrate the region but there might need to be some plasma flow.

Because PFC must be emulsified for use as an intravenous infusion, the concentration of PFC in the emulsion is one determinant of total available gas-carrying capacity. Concentration of PFC in the emulsion can be reported as either weight to volume or volume to volume (v/v). The early emulsions, FC-43 and Fluosol DA 20%, were 10% to 11% v/v emulsions; however, Fluosol was designated 20% because it was 20% w/v. Most PFC pure compounds can carry between 40 to 60 vol% oxygen when equilibrated with 100% oxygen at 1 atmosphere pressure. With these early emulsions being only 10% PFC and 90% emulsifying agent and water, the effectiveness of the PFC was severely limited by the low PFC concentration. Even under the circumstances of the normal emulsion being equilibrated with room air, the available oxygen would have been 0.8 to 1.0 vol%. The total PFC emulsion volume able to be infused to a patient was limited by toxicity issues. In first-generation PFCs, that issue severely limited the amount that could be infused; therefore, although pure PFC has the ability to carry 40 to 60 vol% oxygen, the contribution in patients was quite low. Second-generation emulsions seem to have less toxicity and also have a higher concentration of PFC in the emulsion (40 to 80% v/v) so their ability to contribute to physiological oxygen requirements should be much better.

TOLERABILITY

PFCs in their pure form are biologically inert. No known enzyme system changes these compounds in any way, and there is no measurable fluoride release from them as well (24). The concerns regarding tolerability of the emulsions within biological systems can be separated into two problems. One is that these emulsions are taken up by the reticuloendothelial system and harbored there for some time (25–27). They do have effects on that organ group function.

Second, the emulsion chemistry has inherent effects that have in the past created their own toxicity (28–33).

PFC particles when infused have a variable circulating half-life dependent on the dose and the type of PFC administered. Fluosol has been estimated to have a circulating half-life of between 13 and 24 hours (34–36). The second-generation and third-generation PFCs (perfluoro-octylbromide and perfluorodichloro-octane) appear to have either shorter half-lives of 5 to 9 hours or in the case of the newest one Oxycyte (Synthetic Blood International, Costa Mesa, Calif) 12 to16 hours. In animal models, these half-lives can be considerably extended if high dosages are administered.

After administration, the PFC is equally distributed throughout the circulation and is thought to stay confined to the vascular compartment. Macrophages ingest the PFC, and it is deposited in the liver and spleen (25,32,36). Dependent on the dosage, these organs can actually increase in size and weight within the first 24 hours after a PFC infusion, as the emulsion is deposited there. The emulsion itself is broken down within the reticuloendothelial system, and it appears that the free PFC is slowly carried (by partial pressure solubility) to the lungs and skin (37,38). Most is volatilized and exhaled through the lungs; however, some may transpire through the skin itself. There may be some excretion through the biliary system and thus the fecal route; however, this has not been noted with the second-generation group of emulsions.

The effect that the PFC has on the reticuloendothelial system is a matter of some investigation and potential concern. Once again, the effects of early, first-generation compounds such as Fluosol may be different from those of the second-generation and third-generation compounds. They do appear to cause some swelling of the liver, and there may be some element of dysfunction in some circumstances simply because of mechanical size changes. In Fluosol, there were well-documented increases in liver function enzymes (39–42). Presumably, this would signal that some cell damage or leakage had occurred. For this reason, it was always cautioned not to give Fluosol to patients with liver disease or impending liver failure. However, there was never any indication of these changes persisting beyond several days, and nowhere did patients go on to have liver damage or cirrhosis. In animal studies with the second-generation compounds, although liver swelling and hepatocellular sequestration of PFC can be demonstrated, there is no demonstrable organ damage. Perhaps the elevations of liver function enzymes from the Fluosol were in some way related to the presence of the emulsifying agent pluronic F68 and not just from the mechanical swelling of hepatocytes. Indeed, in animals, as opposed to human work with Fluosol, there is evidence for reduced drug metabolism by the liver, changes in hepatic blood flow, and decreases in microsomal enzyme activity (41,42). In Fluosol-treated animals, hepatic Kupffer cells show reduced phagocytosis and engorgement with PFC (43). The prior anxieties about toxicity from PFC should not unnecessarily cloud the work today with third-generation emulsions.

The fact that some of these same effects are seen in second-generation PFC emulsions (perfluoro-octylbromide and perfluorodichlorooctane) but not to the same severity, even though the second-generation emulsions contain four times the PFC, would suggest that the emulsifying agents in Fluosol somehow contributed to the toxicity. Pluronic F68 is an industrial surfactant with a wide variety of uses. There is evidence that it is not toxic itself but that trace impurities in the actual formulation may have been causing the effects. Neutrophil activation and complement activation occurred with Fluosol and had been attributed to pluronic F68 (30,31). Platelet aggregation is reduced, but complement itself is a platelet inhibitor and may be the cause of that effect (27). The neutrophil activation causes degranulation and suppression of inflammatory responsiveness for a number of hours (32,33,44). It is unclear whether that has any clinical relevance. However, the neutrophil inhibition may be partially responsible for animal findings of decreased reperfusion injury after Fluosol infusion (44). Again, are all these due to pluronic F68? If pluronic F68 is added to neutrophils and incubated, a degranulation situation will occur (32). In the second-generation PFC emulsions, platelet aggregation suppression may still occur with perfluoro-octylbromide but to a lesser degree than seen in Fluosol. Perfluorodichlorooctane appears to have less complement activation than does Fluosol, and in one in vitro study, adding perfluorodichlorooctane to a closed-loop cardiopulmonary bypass circuit actually seemed to inhibit complement formation (45). Both second-generation emulsions do not use pluronic F68 at all but rely on other as yet nondisclosed emulsification processes. They are thought to be quite similar to the egg yolk phospholipid-based emulsifiers used in intralipid preparations (46).

Once the PFC is broken free from its emulsion in the liver and spleen, elimination is dependent only on the volatility of the PFC. Those with high vapor pressures may be in tissues for a considerable length of time. FC-43, with perfluorotributylamine, has a tissue half-life measured in years. Fluosol, a blend of perfluorodecalin and perfluorotripropalamine, has a tissue half-life of 6 days and 63 days, respectively, for the component PFC compounds (47). What is acceptable? We do not have an answer to that question because there are no data regarding any long-term effects of trace PFC within tissues. Second-generation PFCs appear to have considerably shorter tissue half-lives, probably much less than 7 days. However, again it does depend on the dosage administered.

With these organ effects, it is worthy to note that the effects of infusion are met with relatively few side effects. Fluosol has been given to a large number of patients and volunteers both in Japan and in the United States (12,13,27, 32,48,49). A flulike syndrome of mild diffuse muscle aches was noted; however, in some Fluosol patients, chest pains and transient hypotension resulted (50). Facial flushing was also seen. The thought was that these side effects may have been due to macrophage activation and some complement formation (51). The second-generation compounds to date show no evidence of hypotension, although some flulike symptoms may yet be encountered in persons not given any preventative measures (15,16). There are no published safety data as of yet with third-generation compounds.

POTENTIAL APPLICATIONS: OXYGEN TRANSPORT

The creation of a nontoxic, shelf-ready, small particle, stable oxygen-carrying intravascular infusion media may have wide-ranging applicability. Considerable animal and human testing has been done primarily with the 10% v/v compounds such as Fluosol but also with second-generation compounds. A great deal of hope and enthusiasm has been generated, particularly by animal research, yet today PFC emulsions are not yet available for our usage.

Use as a Blood Transfusion Sparing Agent

The efficacy of a single red cell transfusion is difficult to prove (52–56). Recent work has shown that transfusion of banked blood actually decreases oxygen delivery to tissues. Outcome data also seem to demonstrate that transfusions worsen outcomes. Clinicians do not transfuse red cell products when the limits of physiology have been reached (i.e., organ ischemia) but rather do it as a preventative measure. Because the efficacy of a given blood transfusion cannot be proven, it is difficult to show that a replacement for that therapy is also efficacious or even more efficacious. The use of PFC emulsions as a treatment for anemia or prevention of oxygen delivery debt is therefore rather hard to prove as effective. This one problem alone plagues the entire blood substitute technology as it struggles to gain approval from government agencies. The FDA has issued a statement in the last 18 months acknowledging that they will support the blood substitute industry with allowing an oxygen therapeutic to be deemed better if it provides roughly the same amount of oxygen delivery and allows patients to get by with fewer units of blood transfused.

The first use of PFC emulsions was to treat a gastrointestinal bleed in 1980 with Fluosol DA 20% (57). Shortly thereafter in 1982, a study of a series of patients ($n = 185$) was published from Japan (49). Most patients were experiencing surgical blood loss and had refused blood products. No major cardiovascular, biochemical, or anatomical abnormalities occurred in the series of patients. There was a slight leukocytosis and increase in their bleeding time. Some patients had changes in their liver enzymes that were transient. It was thought that the contribution to oxygen-carrying capacity was 1.2 to 1.3 vol%, although this was calculated and not measured. Although this series represented an initial enthusiastic endorsement for PFC emulsions as an alternative to blood, there was no randomized control group with which to compare either outcome or laboratory findings.

A report of another series, this time from China, of war casualties listed 140 patients given PFC (48). Once again, there was no control group that received colloid, crystalloid, or blood with which to compare. These authors did note some side effects, including flushing, chest tightness, a decrease in platelet count, and some changes in liver functions. Were those products of the PFC infusion or the natural course of injuries incurred in wartime?

In the United States and Canada, some small series were reported. One listed seven patients who received up to 3% fluorocrit when undergoing surgical blood loss (48). The contribution to measured oxygen delivery was 0.7 to 0.8 vol%, which the authors thought was not significant enough to warrant further pursuit. Also, patients had to breathe 100% oxygen, and the half-life of only 24 hours was believed by the authors to be insufficient for adequate erythropoiesis to replace the oxygen-carrying function of the Fluosol DA 20%. However, one should point out that if these patients derived some benefit from the added 0.7 to 0.8 vol%, then little erythropoiesis would be needed to replace the effect of the PFC.

A Canadian study was attempted, using Fluosol DA 20%, and only three patients were undertaken, because one had a severe reaction after a test dose (59). Here the authors noted that mixed venous oxygen saturation increased after PFC infusion and concluded that oxygen was being preferentially delivered from the PFC. Once again, no control group or randomization was done with either of the United States or Canadian early experiences. A case report noted the success of a pancreatoduodenectomy in a patient who entered the operating room with a hemoglobin level of only 5 g per dL (60).

In two randomized studies of, respectively, 46 and 52 patients, there were higher oxygen concentrations measured in the group who received Fluosol DA 20% compared with control subjects who received only crystalloid resuscitation (13,61). The survival and hemodynamics were no different between groups and, like the earlier work in the United States, it was concluded that the contribution to total oxygen content by the PFC, although statistically significant, was not worth the effort clinically.

Second-generation PFC formulations underwent testing as oxygen-carrying media in lieu of blood transfusion in the 1990s. In one study using volunteers undergoing surgery expected to have only small blood losses, perfluoro-octylbromide appeared to be well tolerated (16). Unfortunately, the effectiveness of oxygen transport was not assessed. In another where a small series of patients were expected to lose more than 100 mL of blood during surgery, the patients were given perfluoro-octylbromide before blood loss (15) with mixed venous oxygen saturation pulmonary artery catheters and arterial lines. As the blood loss occurred, mixed venous oxygen saturation was stable or increased over the period of time before PFC infusion, yet actual oxygen-carrying capacity of the PFC was not reported.

A great deal of work is yet to be done with second-generation and third-generation PFC infusions during a number of blood loss situations. Massive hemorrhage could be a potential clinical intervention for PFC use. Researching such events is fraught with a wide range of problems (62). If motor vehicle accident victims are to be studied, there may be questions about consent because most of these victims are incapable of communicating. Persons could not be randomized to receive either blood or PFC because withholding blood may be deemed inappropriate. The population is diverse, and the ability to control any hemodynamic or biochemical variable alone may be nearly impossible. Just as this chapter is being written, a hemoglobin-based oxygen carrier is undergoing its pivotal trial in trauma surgery (Northfield Laboratories). Testing PFC, the even more potent second-generation and third-generation emulsions, is effective instead of, or in addition to blood transfusion and may be more easily carried out in the surgical suite. Once again, the questions remain: which cases should one investigate, how should they be randomized, and what product, blood, or crystalloid/colloid, should they receive? These questions and hopefully some meaningful outcome data will be forthcoming in the not-too-distant future. One thing is agreed upon and that is that Fluosol DA 20% is far too dilute to be of great use as a blood substitute alone in the face of acute hemorrhage.

Oxygen Transport for Angioplasty

Coronary angioplasty with stent placement is now used in more patients annually than those having coronary artery bypass graft surgery. During coronary angioplasty, a balloon is inflated in a coronary artery at the site of an atherosclerotic plaque, thus fracturing, stretching, or otherwise dilating the plaque and a stent is deployed. Historically, this technique used catheters that obstructed flow of blood distal to the inflated balloon for some period of time. The obstruction of blood flow would either cause distal ischemia or hopefully be avoided by sufficient flow from collaterals. Short balloon inflations were used to avoid permanent myocardial damage but the effectiveness of the therapy was limited due to the risks of ischemia. Today, there are angioplasty catheters with balloons that allow for some distal flow of blood. However, the inflation of even one of these causes significant flow reduction and can result in ischemia. PFC emulsions might therefore have a unique application if infused distal to such catheters. Fluosol DA 20% has gained its FDA approval for that indication alone. The evidence of its effectiveness is based on the following research.

In dog studies of coronary angioplasty, oxygenated Fluosol DA 20% showed in several studies that it could provide protection from angioplasty ischemia (62–64). Hemodynamic and electrocardiographic indices of ischemia were decreased in the first reported study (62). This was translated into histological evidence of better cellular preservation with Fluosol distal perfusion as compared with no infusion or crystalloid infusion. Interestingly, if autologous blood was infused distal to the catheter rather than Fluosol or no infusion, then subendocardial blood flow was better. There is no clear reason for this, but Fluosol was a profound histamine releaser in dogs and therefore the regional flow differences could have been species-specific. Fluosol alone had a lower viscosity than whole blood, and therefore it created better subendocardial perfusion (64).

Human studies of distal perfusion during angioplasty began in 1985 with the report of a series of 34 patients (65). These patients could tolerate longer balloon inflations with Fluosol infusion than other patients historically not receiving PFC. Other reports noted less echocardiographic evidence of wall dysfunction, and lower lactate production if Fluosol DA 20% was oxygenated and infused at rates up to 60 mL per min distal to the balloon inflation site (65–68). Also, when compared with groups that received a lactated Ringer solution through the catheter, cardiac output was much better preserved with Fluosol (68). In a multicentered trial for the FDA, 245 patients had either Fluosol DA 20% or no fluid infused through the distal part of the catheter (69). Those who received the PFC had less chest pain during inflation, had fewer electrocardiograph indications of ischemia, and had better systolic function by echocardiography. There was no difference in long-term outcome, yet the FDA believed that these advantages were enough to grant an indication. There were no published articles showing it in clinical use.

Reperfusion Injury and Inflammatory Effects

Reperfusion injury is a complex series of events that occurs when tissues are made hypoxic for some period of time and then high-energy phosphate metabolism is shifted toward the breakdown of purines. When these purines are then exposed to oxygen upon reperfusion, that leads to the

production of high-energy free radicals that can cause further cellular damage by destroying intracellular proteins (70–75). The production of high-energy intermediates is both a result of and a stimulus for white cell attraction and upregulation of neutrophil activity. Today, a great deal of work is ongoing with neutrophil activation, attachment molecules, and regulators of white cell activity. It is far beyond the scope of this chapter to attempt to explain the complex process of reperfusion injury, but there has been a significant amount of research suggesting that PFC emulsions may have effects on reperfusion injury (76–82). Once again, much of this research has focused on myocardial injury.

Dog and pig models of myocardial ischemia showed that the amount of tissue made ischemic can be reduced if PFC systemically infused animals breathing 100% oxygen (81, 82). When left anterior coronary ligation was performed, infarct size in dogs is decreased when hemodiluted to 25% hematocrit and PFC is added, compared with those with only hemodilution alone (83). In the pig models, myocardial oxygen content was better with PFC and hemodilution as compared with hemodilution alone with colloid or no hemodilution at all (84). The onset of myocardial ischemia was delayed if Fluosol was infused before a coronary artery snare was placed. If reperfusion of an ischemic bed occurred with Fluosol and blood, that may not necessarily have shown improvement over blood reperfusion alone. However, if prolonged and preexisting PFC perfusion was present, then reperfusion ischemia was reduced. The thoughts were that myocardial ischemia could be reduced by oxygen delivery to tissues that it would not otherwise reach due to the small particle size of PFCs and its ability to enhance diffusion in slow or poorly moving plasma. Perhaps if tissues were never truly made ischemic, then reperfusion injury might be less.

Other studies in which dogs were subjected to 90 minutes of proximal left anterior descending coronary artery ischemia did show effects of Fluosol upon reperfusion. Animals that had PFC added just after reperfusion had better myocardial function, blood flow, and less neutrophil adhesion to their coronary arteries than nontreated animals (82). In another dog study in which Fluosol was infused just before reperfusion, a series of neutrophil function studies were performed (85). Chemotaxis and lysosome release were reduced in animals that received PFC, and it was concluded that the PFC caused a reduction in reperfusion injury that was independent of myocardial oxygen delivery alone during the ischemic period.

Studies of neutrophils in isolated preparations or in cell culture have shown that the PFC may have independent effects (32,44). Neutrophil adherence, cytotoxicity, and lysosome release upon stimulation in vitro was decreased by PFC but not by the emulsifying agent alone (44). Electron microscopic inspection of neutrophils incubated with Fluosol showed that they had ingested the Fluosol because of vacuoles containing PFC (32). It was believed that the neutrophils had phagocytized the PFC particles and therefore were somehow unable to further react to normal stimuli. There still exists some controversy over whether some of the same effects can be created with the emulsion agents. In vitro incubation with pluronic F68 decreased neutrophil adhesion and reaction to stimulation. Also, in a rabbit model in which 30 minutes of myocardial ischemia was followed by reperfusion with either Fluosol added to systemic circulation or the detergent part of the emulsion, both Fluosol and the emulsifier alone did decrease the size of myocardial infarction as compared with the placebo control (86). It should be noted that only when the rabbits were given 100% oxygen did the effects of the Fluosol and the emulsifier become effective. Also, the infarct size was related to the dose of PFC with the higher dosages having a smaller infarct.

Human studies were undertaken in the late 1980s and early 1990s to test the effect of acute intervention with added infused Fluosol DA 20%. A small study using 26 patients used angioplasty within 4 hours of the onset of acute myocardial infarction and randomly assigned them to either intracoronary Fluosol (40 cc per min) or nothing with their angioplasty (87). The group that received the oxygenated PFC showed better improvement of their left ventricular function than those not receiving the Fluosol. Also, myocardial infarction size was reduced in the Fluosol group. Results from this study prompted a much larger study at multiple centers (88). Four hundred thirty patients in the Thrombosis and Angioplasty in Myocardial Infarction 9 Trial were studied with new onset (less than 6 hours) symptoms of infarction. All patients received aspirin, heparin, tissue plasminogen activator, and angioplasty as quickly as possible. Two hundred thirteen of the 430 were randomized to also receive oxygenated Fluosol as an intravenous dose. It should be noted that the maximum dose received was 15 mL per kg, and a great number of patients received far less than that. Also, the Fluosol was not delivered peripherally through the angioplasty catheter at the time of inflation. At 5 and 14 days after infusion and angioplasty, multiple measurements of ventricular function were made, including stress thallium testing. There were no differences in stroke, death, or bleeding, but there were some small but significant decreases in infarct size in the Fluosol group. The PFC patients had less recurrent angina in the immediate postangioplasty period, but this group also suffered more pulmonary edema. This study is not conclusive and can be criticized for not intervening at an early time period (e.g., 1 to 4 hours) with intravenous infusion. Also, the dose of PFC might not be maximal. One certainly wonders how effective it might be to use a second-generation emulsion that is four times as concentrated. Unfortunately, no studies of neutrophil activation

were done to assess the effect of the PFC on reperfusion injury, so the question still remains as to the effect of PFC on inflammatory responses.

In a second-generation PFC, perfluorodichloro-octane, unpublished data from our laboratories does show that the effects of PFC seen with Fluosol in inhibiting some inflammatory processes may translate into the second-generation compounds as well. In a closed-loop model of cardiopulmonary bypass, using fresh human whole blood and the standard bypass system but without any patient, complement levels were studied (45). It is well known that complement levels rise progressively during bypass, presumably as a response to white cell activation (89). Two groups were studied, those with routine crystalloid prime and those who had PFC emulsion added. The group with the PFC added had no rise in complement during the bypass run. Unfortunately, the reason for this was not given, and a good deal of work remains to be done to understand the effects of these newer PFCs on neutrophil activation.

Organ Protection: Cardioplegia and Transplantation

During cardiopulmonary bypass, usually the aorta is cross-clamped and blood flow to the heart is stopped for an extended period of time. If some attempt to preserve cellular integrity is not undertaken, then myocardial infarction will result. It is impossible to discuss the various recipes and methods for delivering cardioplegia solutions because the types and applications of these solutions are quite variable from one institution to another. Preservation of organs for transport ex vivo and transplantation has had fantastic growth and development in the recent past. Once again, there has been widespread use of newer preservative solutions that have extended the time wherein solid organs can be outside the body and ischemic. Both techniques, cardioplegia and organ preservation for transplantation, are undertaken because there is no present way to continuously supply oxygen and metabolic substrates during the period of time in question. PFC emulsions, with their potential oxygen-carrying capacity, would seem to be perfect for fitting the role of organ preservation.

Heart transplantation has a limiting ischemic time of approximately 6 hours, and the organs are usually preserved with cold crystalloid infusion. Ideally, a system of continuous perfusion with a solution capable of transporting oxygen and containing metabolic requirements would be created. In heart transplantation, a trial of perfusion with Fluosol DA 20% had earlier heart failure, more lactate production, and an increased creatinine phosphokinase than those given colloid alone (90). The mechanism behind this potential failure is unknown, but if PFC is added to albumin, then some of these problems can be reduced (90). Multiple studies have shown in isolated animal organs that kidney, liver, pancreas, intestine, and some other heart protocols can preserve tissue with continuous or intermittent flushes of PFC (91–98). To date, however, there are no series using PFC as their primary solution for transport in human transplantation and no series using the newer second-generation PFCs in either animal organ preservation or in humans.

AIR EMBOLISM

Venous air embolism occurs during sitting craniotomy in probably upward of 40% of cases and is also common in total hip arthroplasty (99–101). Other surgeries have been noted as significant as well, including spine surgery, pelvic surgery, hepatectomy, and neck dissection. The effects of air embolism are dependent on the size of embolus entrained, the speed and site of entrainment and the eventual distribution of the air. A significant number of patients have a probe patent foramen ovale that, under the right circumstances, can lead to movement of the air from the right side of the heart to the arterial side (102). Hypotension, adult respiratory distress syndrome (ARDS), coagulopathy, stroke, and death are all possible consequences of venous air embolism. To date, there is no adequate treatment modality other than physical maneuvers to move the blockage to the circulation caused by the embolism (103).

Arterial air embolism can be caused by venous air embolism and migration through a patent foramen ovale. In cardiopulmonary bypass, massive air embolism is a rare but almost universally fatal complication caused by air entering the arterial side of the circuit (104). Smaller amounts of air embolism, including microair embolism, are much more commonly seen (105,106). During cannulation of the aorta and decannulation, air is entrained. Open cardiac procedures such as valve replacement, congenital repair, or thoracic aneurysm repair, by necessity of opening the vasculature, have a large chance of distributing air emboli. Even coronary artery bypass graft surgery has a large number of microemboli associated with it. The cardiopulmonary bypass machine, because of its mechanism with pressure changes, causes the formation of microbubbles. These microbubbles have often been implicated as a possible primary cause of neuropsychological dysfunctions (105–109). Forty to eighty percent of patients 7 days after cardiopulmonary artery bypass have one or more abnormalities on exacting tests of cognitive abilities, learning, and complex higher cortical function (110). These abnormalities persist in 20% to 40% of patients. Similar types of microair emboli occur during decompression sickness, and indeed the same types of neuropsychiatric changes can be seen in divers who have experienced "the bends" (111).

PFC emulsions have a unique ability not only to solubilize oxygen but also to carry nitrogen and other gases that would not be soluble in plasma. Indeed, nitrogen is ten thousand to one hundred thousand times as soluble in PFC as in plasma (17). A number of studies have shown promise that PFC emulsions may be useful in both venous and arterial air embolism (112–121).

In decompression sickness, a number of rodent models have been tested in which animals have been compressed to six or more atmospheres in room air and rapidly decompressed, with resultant air embolism (114,117). Immediate treatment with a PFC (FC-43) and 100% oxygen has shown PFC to be effective in preventing death (114). In dogs, a xenon solubility study has demonstrated that PFC can greatly speed the removal of xenon, a very insoluble gas, from muscle tissue (119). It was estimated that the removal of xenon in animals treated with PFC was at least seventeen times as quick as that seen without PFC. It was also estimated that the removal of nitrogen from such tissues, because of physical chemical properties of the PFC, could cause the removal at least four times as fast as that of xenon. These studies were performed with first-generation PFC and one wonders if the efficacy would be even greater if a second-generation emulsion were used. To date, no human trials of prevention or treatment of decompression sickness have been performed with second-generation PFC.

Venous air embolism has been studied in several animal models with first-generation PFC (FC-43). A rabbit study looked at survival in animals pretreated with PFC or hetastarch and ventilated with either room air or 100% oxygen (112). Venous air embolism was delivered via the femoral vein continuously until death and the time until death noted. Animals who received PFC and were mechanically ventilated with 100% oxygen lived five times as long as all other groups of animals. In a larger animal study, cardiac and pulmonary hemodynamics were monitored in dogs pretreated with PFC (113). Again with femoral venous air embolism there were fewer hemodynamic complications in the dogs pretreated with PFC. The pulmonary artery pressures and cardiac outputs suggested that the air embolism in the PFC group was smaller or caused less mechanical obstruction than the one in the control group.

Arterial air embolism has been examined in cerebral and coronary artery air embolism. In rats given either a continuous air infusion in their internal carotid artery or a large bolus of air, those pretreated with PFC (FC-43) lived longer, had earlier return of their electroencephalograms, and had fewer ataxic events than animals pretreated with hetastarch (115). In a dog study with the left anterior descending coronary artery isolated and cannulated, 0.1 mL per kg of air was injected (116). Those animals that had again received a first-generation PFC before air embolism had fewer ventricular arrhythmias and quicker return of dP per dT than animals preloaded with colloid. In a recent work using swine and a second-generation PFC as an additive to the cardiopulmonary artery bypass machine, a model of massive air embolism was performed (122). Animals given Oxygent® (Hemogen Inc., St. Louis, Mo) as compared with colloid had better cerebral blood flow and higher electroencephalograms in the first few minutes after going onto bypass. The mechanism for these differences still is not completely understood, but others have suggested that the PFC actually will increase cerebral blood flow. One recent study using a hemoglobin blood substitute did not show the same increases in cerebral blood flow. The swine model previously described used a massive air insult of 5 mL per kg injected directly into the common carotid artery 10 minutes after bypass. Endpoints were cerebral blood flow by calorimetric microspheres, electroencephalography, and infarction by triphenyl tetrazolium chloride stain 6 hours after insult. The cerebral blood flow was significantly better in the PFC group and the electroencephalogram did not fall as low in the PFC group and had a more rapid return to baseline. The infarct data showed that four of six animals in the colloid group had diffuse infarctions and no PFC animals showed any infarcts. In a treatment protocol, treatment of massive air embolism is clearly far less effective than priming the bypass machine with PFC.

Microembolism to the brain and systemic circulation can be assessed by viewing the retinal microcirculation (123,124). Retinal fluorescein angiography has demonstrated that 3% to 5% of the capillaries are not perfused at the end of bypass and that by 1 day later, these are reperfused. In a dog study using the same retinal angiographic technique, if the cardiopulmonary bypass machine is primed with a second-generation PFC, the amount of capillary obstruction is decreased by 90% or more. In the swine model of massive air embolism, another set of studies using retinal angiography has shown about a 50% reduction in capillaries blocked if PFC is used in the prime and furthermore correlations by histology staining showed better preservation of capillary blood flow and less endothelial damage (unpublished results from our laboratory).

Liquid Ventilation

The initial work showing rodents breathing oxygenated liquid PFC led to speculation that such technology could be used in deep sea escape. Today, application of liquid PFC breathing shows promise in infant respiratory distress and ARDS (125–128). Both syndromes have severe problems with systemic oxygenation. There is a tremendous loss of alveolar activity with either loss of surfactant or diffuse

inflammatory infiltrates that fill the alveolar spaces. Clearly, not all ARDS or respiratory distress syndromes are the same, and there is not only a continuum of severity but also a multitude of causes in the ARDS situation. Today, two methods are being investigated to assist in these syndromes. Liquid PFC ventilation involves filling the entire respiratory tree with PFC and then using some piston-driven ventilator device to move the liquid. Without a unique ventilator, the work of breathing would be so great as to make it impossible for these otherwise severely ill patients to respire. Animal studies have shown some promise with liquid PFC ventilation, and one early report showed some transient improvement in infants who had failed every other therapy (125). As yet unpublished ongoing trials of this technique are underway.

PFC associated gas exchange may be useful in ARDS more so than infant respiratory distress. The technique uses just enough PFC to fill the functional residual capacity. It thereby is thought to coat the alveolar spaces, perhaps working as a surfactant and also improving gas exchange across the alveoli. Animal models have shown good hemodynamic tolerance and improvement in compliance and gas exchange (126,127). Once again, large-scale clinical data are not yet available.

RADIOLOGY APPLICATIONS

The PFCs may have some advantages because they can produce vascular contrast in a number of imaging techniques (129–131). If bromine or iodine is part of the PFC molecule as in perfluoro-octylbromide, then some amount of x-ray contrast is conferred. In rabbits with abdominal tumors who were infused with perfluoro-octylbromide, the tumors could be imaged more easily. Magnetic resonance imaging (MRI) has a number of advantages that routine x-ray does not have (131). There are presently no adequate MRI dyes, and PFCs may fill that role. The MRI can be tuned to a frequency that interrogates fluorine molecules, and also the PFC does not contain any hydrogen ion. MRI usually is tuned to hydrogens, and therefore the PFC can act as a negative contrast. Once again, future work is needed to see whether this can be developed as an advantage or whether it will be a potential problem. If PFC is infused as a blood substitute and a patient needs an emergency MRI or computed tomography, one can conceive of a scenario in which present technology has difficulty with the PFC in the vascular tree.

TUMOR THERAPY

Chemotherapy may be more effective in some tumors if oxygen is delivered effectively to that tumor (132). Tumors may have areas of poor capillary distribution that makes chemotherapy less effective. Also, radiotherapy is most effective in well-oxygenated tumors. PFCs with their ability to deliver oxygen to areas that may have poor perfusion otherwise theoretically would lend themselves to assisting tumor therapy. In animal models using both first-generation and second-generation PFC emulsions, there is considerable benefit to combining the chemotherapy and PFC. Although human trials are just now underway, this idea does seem encouraging. Also, there are considerations of housing the actual chemotherapeutic agents within the emulsion particle itself, thereby combining the delivery of oxygen and adjuvant therapy at the same time. Certainly, much work needs to be done before PFC is routinely seen as part of cancer therapy.

1998 TO 2005

It would seem as though the PFC saga has its cyclical successes and failures. The period form 1998 to the present has been one of frustrations in the PFC industry. Unfortunately many of the blood substitute companies, although calling themselves oxygen therapeutics, still tried to go head-to-head with a unit of banked blood. Such thinking has led to some rather bizarre and totally contrived schemes to make sure that patients would receive either banked blood or the PFC emulsion. Severe autologous normovolemic hemodilution was utilized in several studies. Alliance Pharmaceuticals utilized sudden severe euvolemic hemodilution prior to cardiopulmonary bypass in a pivotal phase three study of Oxygent® versus allogeneic blood for coronary artery bypass surgery. The company even conceived of the use of PFC as a way to enhance euvolemic hemodilution and patented it as an application for their compound. The study was stopped after finding a higher stroke rate in those patients receiving the PFC. Both stroke rates were within the accepted limits for the procedure (CABG surgery), but the fact that the stroke rate was statistically higher in the PFC group gave both the company and the FDA reason for concern. Since that time Alliance has retrenched its investigations of Oxygent®. The European Agency for the Evaluation of Medical Products (EMEA) has recommended that Alliance cease its attempts to compare a PFC to a single unit of banked blood. This seems most reasonable in light of all the research presented in this chapter. The corporate world has demanded to have these products called oxygen therapeutics. It now seems as though future research will focus upon them as exactly that, ways to supply enhanced oxygen delivery to tissues at risk.

Recent work utilizing the Alliance product has continued to show that it does provide organ protection. In the

face of severe decompression sickness it increases the removal of whole body nitrogen loads as well as increases the breath per breath removal of nitrogen in a swine model. It provided the first experimental method for treatment of decompression sickness without recompression of a victim (swine model) (133,134). Ongoing investigations are underway sponsored by the United States Navy to investigate the mechanisms demonstrated in this protection. It is as yet unclear whether the use of PFC in treatment/prevention of decompression sickness is due to enhanced oxygen delivery to tissues at risk or due decreased bubble formation or early dissolution. Work by the United States Navy and our laboratories is presently investigating whether unique methods of utilizing PFC at depth before surfacing could prevent decompression sickness.

The formation of microbubbles is a major hazard in cardiac surgery. Already reported work in this chapter notes that a second-generation PFC can remove or prevent large percentages of microbubbles from the cardiopulmonary bypass machine (122). This work appears somehow hard to reconcile with the Alliance findings of increased stroke rate in their pivotal study. In both our work and in work from Duke University it was found that PFC increases cerebral blood flow. Other and more recent work from our institution shows that PFC (Oxygent®) preserves brain function in models of traumatic brain injury. When the PFC is given immediately after a standard concussive water hammer hit to the skull there is preservation of mitochondrial activity, better cellular redox function and decreased tissue destruction (135). For this reason we have actually proposed the use of PFC as an initial intervention in traumatic brain injury.

Work with PFC in an ex vivo model of animal sickle cell disease has shown that when oxygenated PFC is infused the microvascular obstruction can be reversed (136). Peripheral vascular resistance, as a measure of vascular obstruction was returned to baseline with PFC infusion into animals undergoing a sickle crisis. Vascular wall shear rates show that sickled red cells are released from vascular endothelium where they have lodged.

The Russians do have a PFC emulsion available on their market. Perftoran, a Russian based company, which makes a first generation emulsion by that same name was approved and registered in Russia in 1996 for use. This is essentially the same PFC as old Fluosol® in that it contains the same carbon chains and is at the 10% volume concentration. It does use a less toxic emulsifier than Pleuronic F68. In Russia over 2,000 patients received the agent in trials. Of interest the Perftoran has to be thawed and sonicated just the same way old Fluosol® had to be prepared. However, it is felt that it can be thawed and prepared up to 5 weeks in advance of infusion.

Another offshoot of the relative success of Fluosol® is the company Sanguine, Pasadena, California. They are founded by some of the same people that drove the development and successful FDA approval of Fluosol®. They have a second-generation emulsion using modern emulsion technology but similar fluorocarbon compounds to Fluosol®. The new, much more highly concentrated solution has undergone some animal toxicity testing but to date has not started large scale human research. At the present time it is named PHER-02. When it will begin human safety and efficacy testing is unclear.

Synthetic Blood International is the last of the companies presently involved in PFC emulsion research. They are based out of Costa Mesa, California, and have a product named Oxycyte® which is a 60% volume emulsion with a .19 micron diameter. Its fluorocarbon is F-tert-butylcyclohexane in a modern lipid emulsion. It is now undergoing phase II trials in orthopedics but significant laboratory work on organ protection is also being investigated.

SUMMARY

The quest for a safe, economic, and effective blood substitute continues. The PFC emulsions have shown some promise, but initially their effectiveness was limited by the imperfect emulsion chemistry. Early 10% v/v emulsions could not supply enough tissue oxygen delivery to warrant their approval for use as whole body oxygen delivery media. However, second-generation compounds have a four times greater concentration of active compound and therefore are quite effective. Also, second-generation compounds appear to have a better side-effect profile. These and PFC emulsions are now in extensive human testing.

Perhaps the most exciting applications of second and third-generation compounds go beyond merely enhancing oxygen delivery. Insoluble gases will become considerably more soluble if PFC is added to human blood. Problems that used to plague us, such an air embolism or decompression sickness, may become treatable or preventable. Also, use of radiology dyes and cancer adjuvant therapies will develop in the next few years. No matter what the eventual development of PFC infusions will be, they will be considerably different from infusing a unit of packed red blood cells or even a polymerized hemoglobin preparation. Indications, contraindication advantages, and limitations will become evident. It does appear that the corporate world has finally realized the failures of their past. They are embracing and now financing research into organ protection and understanding these compounds to be oxygen delivery devices. Perhaps with such a modern and realistic view of their applications, PFCs will actually make it to the marketplace. This is a very exciting and potentially revolutionary group of compounds.

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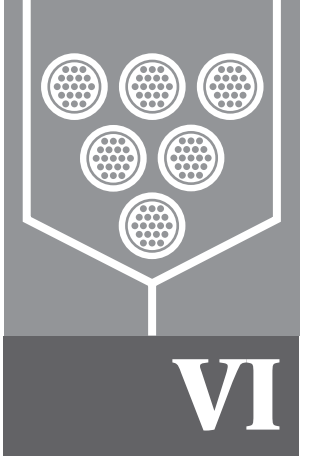
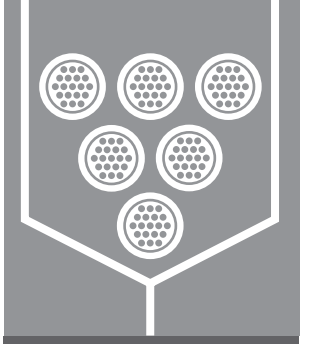


Trauma and the Bleeding Patient



21

Initial Resuscitation of the Hemorrhaging Patient

Richard P. Dutton

Few patients are as challenging as the one with uncontrolled hemorrhage, as few situations are so immediately life-threatening. Acute hemorrhage is the second leading cause of death from injury (after traumatic brain injury), and a leading cause of mortality related to all surgeries (1). More than 100,000 Americans die each year from perioperative exsanguination, and countless others die from multiple organ system failure triggered by an episode of hemorrhagic shock.

Initial resuscitation of the hemorrhaging patient requires close monitoring of physiologic parameters during the dynamic process of diagnosis and treatment. Resuscitation is the responsibility of emergency medicine physicians, surgeons, anesthesiologists, and intensivists often forced to make complex decisions with a minimum of information. Understanding the physiology of shock and the implications of various treatment strategies is essential to achieving good outcomes in this difficult patient population.

While the anatomy of surgical hemorrhage does not change, knowledge of the physiology of hemorrhage and the ideal strategy for resuscitation has continued to evolve. New equipment, fluids, medications, and thinking have all been introduced within the past decade, forcing radical changes in patient management. And as exciting as the recent past has been, the immediate future promises even more. Researchers are just beginning to describe individual genetic and proteonomic responses to hemorrhage, leading to the possibility of patient-specific treatment algorithms based on the manipulation of ischemic mediators only recently known to exist. This chapter will outline the basics of early resuscitation, emphasizing existing controversies and emerging therapies, with support from the current scientific literature.

DIAGNOSIS OF HEMORRHAGE

Successful resuscitation from hemorrhagic shock begins with control of the source of the problem, the hemorrhage itself. Perioperative hemorrhage arises in one of two ways. In scheduled surgical procedures blood loss may be an anticipated event that is necessary for completion of the surgery. Even the most meticulous surgical technique cannot prevent all blood loss from certain procedures (i.e., liver transplantation), and in the patient with cirrhosis or a congenital coagulopathy, the expected blood loss may be substantial. This sort of perioperative hemorrhage is distinguished by two features. First, hemorrhage can be controlled by aborting the surgical procedure, minimizing it, or completing it in stages. Second, perioperative hemorrhage from scheduled surgical procedures can be anticipated, and the patient appropriately prepared. This includes everything from the anesthetic technique (e.g., adjuvant epidural anesthesia), to provisions for autologous blood donation, to the maintenance of a euvolemic state prior to the onset of hemorrhage. Preparation for bleeding can make a huge difference in outcome because anticipated hemorrhage can be preceded by anesthesia, which has been shown in animal models to improve the outcome from acute hemorrhage (2).

Hemorrhage can also occur as the result of trauma or sudden medical disease (such as gastric ulceration). In this case shock is already established prior to resuscitation and may be the first sign of hemorrhage. The patient is awake and may be in pain. The source of bleeding is more likely to be cryptic, and the patient's response to hemorrhage may be complicated by alcohol or other street drugs, or prescription medications such as beta blockers or warfarin. A trauma patient requiring transfusion of more than 10 units of packed red blood cells (about one blood volume) has a prospective mortality of 39% in one recent report, (3) as compared with less than 5% for major elective surgery patients requiring the same amount of blood.

Typical adult human blood volume is 70 mL per kg of lean body mass, meaning that the average adult male has a total blood volume of approximately 5 liters. A loss of less than 20% of this total (1 liter) is generally well tolerated, with few long-term physiologic consequences. Blood loss of 20% to 40% will cause vital signs to change and evidence of impaired tissue perfusion will become apparent in laboratory assays. Loss of greater than 40% of the blood volume will result in frank hemorrhagic shock, manifested by the symptoms in Table 21.1, and will progress rapidly to circulatory system failure and cardiac arrest if not corrected (4).

Hemorrhage sufficient to endanger a patient's life occurs in one of 5 compartments (Table 21.2) (5). While the source of bleeding will be obvious in elective surgeries, there are many other cases—including most traumas—where the source of hemorrhage must be identified before definitive treatment can begin. Nothing should be allowed to interfere with diagnostic and therapeutic steps to control hemorrhage, but resuscitation must perforce begin while these steps are still underway, and must be conducted in such a way that it does not cloud the diagnostic picture or exacerbate bleeding.

TABLE 21.1
SIGNS AND SYMPTOMS OF SEVERE HEMORRHAGIC SHOCK (LOSS OF > 40% OF THE BLOOD VOLUME)

- Agitation, progressing to lethargy and coma.
- Pallor and diaphoresis.
- Decreased blood pressure; narrowed pulse pressure.
- Tachycardia (not universally present).
- Tachypnea.
- Cold extremities; inability to detect pulse oximeter signal.
- Diminished urine output.
- Diminished capillary refill; loss of skin turgor.
- Progressive anemia.
- Increased serum osmolarity.
- Acidosis.
- More negative base deficit.
- Increased serum lactate.
- Decreased mixed venous oxygenation.
- Increased sublingual or gastric CO_2 level.

TABLE 21.2
POTENTIAL SITES FOR EXSANGUINATING HEMORRHAGE

Site	Diagnostic Tests	Treatment
Chest	Physical exam Chest x-ray CT scan	Tube thoracostomy Surgery
Abdomen	FAST CT scan	Angiographic embolization Surgery
Retroperitoneum (usually pelvic)	CT scan	Angiographic embolization Pelvic fixation
Thighs (long bone fracture)	Physical exam	Orthopedic fixation
External	Physical exam Paramedic report	Direct pressure Arterial ligation Surgery

CT,computed tomography; FAST, focused abdominal sonography for trauma.

Hemorrhage is diagnosed by direct observation of blood loss, as from open wounds in the emergency department (ED) or operating room (OR), by laboratory assay and by diagnostic studies. Reduction of the hematocrit is the traditional marker for hemorrhage, because fluid volume losses are rapidly compensated for by mobilization of extracellular fluid into the vascular space and by intravenous crystalloid administration, whereas red cell mass will decrease in proportion to hemorrhage. In cases of rapid hemorrhage, however, the initial hematocrit measurement may be misleading, because the patient is losing whole blood. This is especially true in traumatic hemorrhage, prior to the start of intravenous resuscitation. Hypovolemia may be indicated by an increase in serum osmolarity, while progressive metabolic acidosis, an increased serum base deficit, and elevated lactate level characterize hemorrhagic shock.

The source of hemorrhage may be obvious on physical examination, if it is due to an open wound or palpable long-bone fracture. While most superficial and extremity bleeding will resolve spontaneously, large volumes of blood can be lost from scalp lacerations, associated vascular injuries, and in patients with underlying coagulation disorders. Hemorrhage in the thorax is usually accompanied by shortness of breath, and a hemodynamically significant bleed in this compartment will be readily apparent on chest x-ray or computed tomography (CT) scan. Focused

abdominal sonography for trauma (FAST) is the preferred diagnostic modality for abdominal hemorrhage (6). Free intraperitoneal fluid is readily apparent on ultrasound examination and can be assumed to represent hemorrhage in most patients. Hemodynamically unstable patients should undergo emergent exploratory laparotomy. Those who are stable are further assessed by CT; isolated hepatic or splenic trauma may be managed with angiographic embolization if the rate of hemorrhage is slow (7). Retroperitoneal hemorrhage is the hardest to diagnose, as this compartment is only well visualized by CT scan and is difficult to access surgically. The most common source of a retroperitoneal bleed following trauma is disruption of the sacral venous plexus. This diagnosis should be suspected in any patient with a grossly unstable pelvis or a radiographically apparent fracture of the posterior pelvic elements.

PATHOPHYSIOLOGY OF HEMORRHAGIC SHOCK

Loss of blood volume and the onset of cellar ischemia trigger multiple changes throughout the body. Pain, cognitive perception of an injury, and reduction of cardiac preload activate the fight or flight response. Sympathetic outflow and catecholamine release cause constriction of nonessential vascular beds, increased cardiac inotropy, and release of hepatic energy stores (8). Physiologic compensation by selective vasoconstriction, increased heart rate and contractility, and fluid uptake from the extracellular, extravascular space will allow for preservation of cardiac output and blood pressure in the initial stages of hemorrhage. If hemorrhage resolves spontaneously or is externally controlled before significant blood loss occurs, then the mild to moderate shock state that develops may not be clinically apparent, as it is rapidly corrected by intravenous fluid therapy (Fig. 21.1, curve A). The patient with an isolated femur fracture is a good example of this state; although a 1 to 1.5 liter blood loss is associated with this injury, spontaneous hemostasis will usually occur. It is unusual for this patient to be hemodynamically unstable at the time of ED arrival.

Persistent hemorrhage will overwhelm the capacity for systemic compensation, leading to a downward spiral of pathophysiology (9). Decreased oxygen delivery at the cellular level leads to anaerobic metabolism, fluid uptake from the extracellular space (exacerbating hypovolemia and obstructing capillary flow), cellular hibernation, and eventual necrosis or apoptosis (10). Cellular ischemia results in the release of inflammatory mediators and metabolic byproducts into the circulation. These agents are both direct and indirect poisons, causing a loss of cardiac and vascular contractility that leads to a further reduction

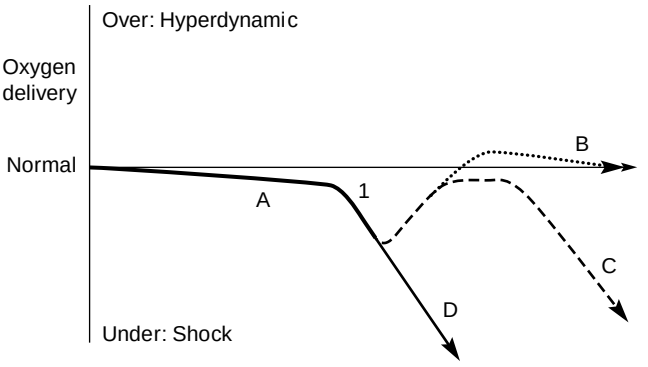


Figure 21.1 Potential outcomes from an episode of hemorrhage, represented by changes in tissue oxygen delivery over time. Curve A represents the compensated patient with limited blood loss and subsequent re-equilibration. Point 1 marks the point when normal physiologic compensation fails. Curve B represents the patient with transient uncompensated shock; increased oxygen delivery over normal to payback oxygen debt is common following control of hemorrhage. Curve C represents the patient in whom hemorrhage control has occurred, but a lethal shock cascade has been triggered; this patient develops multiple organ system failure and ultimately dies. Curve D represents the patient who develops an acutely lethal shock state and fatal cardiovascular collapse due to failure of timely hemorrhage control.

in cellular oxygen delivery. Acute irreversible hemorrhagic shock (Fig. 21.1, Curve D) occurs when the vasculature itself has insufficient energy reserves to maintain a vasoconstricted state. Development of the lethal triad of acidosis, coagulopathy, and hypothermia heralds the failure of resuscitation (11). The circulation becomes unresponsive to volume loading and catecholamine stimulation, inappropriate vasodilatation occurs, and the patient dies. While mortality from hemorrhage outside the hospital is due to an abrupt fall in cardiac output and immediate coronary ischemia, mortality during treatment is characterized by vascular cell failure despite ongoing restoration of blood volume.

The shock sustained by an individual patient is a summation of the time over which hypoperfusion occurs and the depth of the deficit in oxygen delivery. Figure 21.1 illustrates this concept and the potential outcomes. Mild, compensated shock and severe irreversible shock are unlikely to be impacted by treatment. Between these states, however, lies an important middle ground in which the speed and precision of resuscitative care has a strong influence on the patient's outcome. Control of hemorrhage is the most important therapeutic goal, because otherwise resuscitation is inevitably futile. Once systemic compensation is exceeded, and the shock spiral begins to wind down, there is a short window of time in which resuscitation is still possible if bleeding is controlled (Fig. 21.1, Curve B). This is the physiologic underpinning of the golden hour concept of trauma care, and

the focus of the Advanced Trauma Life Support course of the American College of Surgeons (4). Once hemorrhage is controlled, the outcome of an episode of shock is influenced by the rate and precision of fluid resuscitation, the cellular response of individual organ systems, and the balance of inflammatory mediators over the subsequent hours and days. Patients may survive acutely only to die days to weeks later of multiple organ system failure (MOSF) triggered by the initial dose of shock (Fig. 21.1, Curve C).

Cerebral or cardiac ischemia is rare in survivors of acute shock, because the body's compensatory mechanisms are focused on preservation of perfusion to these systems up until the terminal moment. Primary ischemia of the pulmonary system is also unlikely, as cells have direct access to an oxygen supply. The lungs are the sentinel organ system for the secondary effects of shock, however. Toxins and ischemic mediators pass directly to the lungs from the systemic circulation, triggering the systemic inflammatory response syndrome (SIRS) that follows severe shock (12). While some degree of inflammation is important in the recovery from tissue injury and shock, the release of cytokines and free radicals may also be destructive to individual cells and organ systems. With the failure of most clinical trials focused on manipulation of a single component of the inflammatory cascade (Activated Protein C being a notable exception) (13) it has become apparent that it is the appropriate balance of dozens of mediators over time that must be medically managed, in accordance with the individual patient's age, history, injuries, and genetic make-up.

Ischemic cells of the gut and liver become edematous, and may ultimately choke off their own capillary networks (14). This no reflow phenomenon can cause persistent ischemia and ultimately necrosis even following the restoration of normal systemic blood flow. Hepatic dysfunction is marked by irregularities in glucose control and production of coagulation factors, while intestinal ischemia leads to a loss of barrier function and the increased translocation of bacteria into the portal circulation (15). Renal ischemia results first in cellular hibernation, with a decrease in active filtering, followed by acute tubular necrosis (16). Renal failure following severe shock is usually not permanent, although the need for extracorporeal hemofiltration is frequent in the short term. Skin, muscle, and bone are the most resistant tissues to acute shock and can tolerate the longest periods of hypoperfusion before becoming ischemic. Muscle and other soft tissue cells that have been directly injured or ischemic will take up extracellular water, contributing to the need for resuscitative fluids following shock (17). Because of the mass of tissue involved, muscle ischemia also contributes substantially to the volume of lactic acid and other metabolic byproducts resulting from a period of hypoperfusion.

CONTROL OF HEMORRHAGE

Once the source of hemorrhagic shock has been identified, achieving hemostasis becomes the overwhelming priority. The most obvious interventions begin with emergent exploratory laparotomy or thoracotomy, and include resection of severely injured tissue, ligation and cautery of open vessels, and tamponade of surface bleeding. Damage control surgery refers to a strategy of prioritizing the control of hemorrhage ahead of restoration of anatomic integrity (18). Damage control is indicated for any patient in severe shock, and is the norm in the initial exploratory surgery for an unstable patient. Badly injured organs such as the spleen or kidney are simply removed. Damaged bowel, liver, or lung are resected by staple. Injured veins and peripheral arteries are ligated. Organ surface or soft tissue bleeding is controlled with the application of a topical thrombin preparation and a collagen mesh, followed by packing with sterile gauze. Once gross hemostasis is achieved the chest or abdomen is not surgically closed, but is sealed with a sterile dressing. The patient is transferred to the intensive care unit, where resuscitation is completed and any necessary diagnostic studies are performed. The patient is returned to the OR in 24 to 48 hours for re-exploration, restoration of bowel and vascular continuity, and more definitive closure of the surgical wound.

Evolution in equipment and techniques have increased the role of angiographic embolization in the management of acute hemorrhage (7). Embolization can achieve direct hemostasis of injured arteries and by reducing pressure and flow to a particular organ system, it can also contribute to the spontaneous resolution of venous plexus bleeding. Angiography and embolization are indicated as the primary therapy for hemorrhage in surgically inaccessible regions, such as the posterior face and base of the brain and the posterior pelvic bowl (19). Angiographic embolization is also helpful as an adjuvant therapy in the management of hepatic, splenic, and paraspinal hemorrhage. It is common to move directly from the OR to angiography following a damage control laparotomy, to complete hemostasis in the trauma patient with multiple complex injuries. Major trauma centers are set up to continue resuscitation in the angiography suite, but in smaller hospitals this may require considerable logistic effort.

Nonsurgical options to encourage hemostasis consist of careful management of blood volume and composition, with the goal of preserving native hemostatic mechanisms. Maintaining a low blood pressure and avoiding

excessive dilution of the blood will help to minimize rebleeding in the patient with tenuous early clots (20). At the same time, enough resuscitative fluid must be administered to avoid or minimize systemic acidosis and to provide an adequate supply of clotting factors and platelets. Body temperature must be kept in the normal range, as hypothermia will substantially exacerbate coagulopathy and acidosis.

Finally, anecdotal reports of the use of recombinant activated human coagulation factor VII (FVIIa) have raised the possibility that medical therapy can substantially impact the course of acute hemorrhagic shock (21,22). FVIIa promotes and amplifies cell-based coagulation in the presence of tissue factor exposed at the site of vascular disruption. In the presence of an adequate supply of platelets and thrombinogen, FVIIa will produce hemostasis in patients who have become coagulopathic from acute hemorrhage and will facilitate the localization and repair of surgical bleeding. Preliminary results from a randomized, prospective trial in hemorrhaging trauma patients indicated a reduction in transfusion requirement following FVIIa administration, with no evidence of increased thrombotic complications (23). The expense of this therapy will limit its application in the near term to patients with severe hemorrhage, but over time the systemic administration of procoagulant agents will likely become an important component of initial resuscitation.

Fluid Resuscitation Strategy

Rapid administration of fluid and blood products to support systemic perfusion may promote increased hemorrhage or rebleeding from previously hemostatic areas by one of several mechanisms (24). Increased preload leads to increased myocardial contractility and elevated blood pressure, which may overwhelm the hemostatic capacity of fragile early clots. Increasing preload will also tend to reverse vasoconstriction in injured tissues, leading to hemorrhage from vessels that were initially vasospastic (25). Crystalloid infusion in response to hypotension will dilute the red cell mass and the clotting factor concentration of the blood and will cause hypothermia absent the attentive use of warming devices. Rebleeding is characteristic of the transient responder in the ED. Initial hypotension responds to crystalloid infusion, but rebleeding occurs, followed by recurrent hypotension. Thus necessitating the use of more fluid, and so on, until either definitive hemostasis is established or the shock becomes so great that the patient dies.

Avoidance of crystalloid resuscitation and titration of resuscitation to a lower than normal blood pressure have been studied as therapeutic options in the acutely hemorrhaging patient, with a suggestion of benefit (26,27). The difficulty with advocating this approach lies in the lack of effective monitoring for tissue perfusion in the chaos of the ED or OR, while all efforts are being directed toward the diagnosis and treatment of uncontrolled hemorrhage. Underresuscitation may decrease active bleeding and facilitate control of hemorrhage, but runs the risk of increasing systemic ischemia and the incidence of organ system failure. More rapid administration of fluid will increase perfusion in the short term, but worsen hemorrhage and transfusion requirement in the long term. Proponents of each approach have claimed benefit in reducing mortality and organ system failure, but a convincing clinical study has yet to be published.

Table 21.3 lists resuscitation targets for the patient with active ongoing hemorrhage. A lower than normal blood pressure (80 to 90 systolic) is advocated for patients in whom it is likely to be well tolerated. This includes young, previously healthy trauma patients, but excludes those with traumatic brain or spinal cord injury, those with underlying cardiac dysfunction (including the elderly), and those with preexisting disease states, such as diabetes, that are characterized by end-organ ischemic complications. Emphasis is placed on close monitoring of systemic perfusion, as indicated by the pH, base deficit, and lactate concentration of serial arterial blood gas samples. Increase in systemic acidosis is an indication for increased fluid administration, while stable or improved values indicate that deliberate hypotension is tolerable and should continue until hemorrhage is controlled.

It is likely that the next decade will see the clinical application of noninvasive monitors of tissue oxygenation that can continuously guide resuscitation, even early in the clinical course. Cardiac output and mixed venous oxygenation as measured continuously by a pulmonary artery catheter are very useful parameters, (28) but frequently not available until central intravenous access can be spared

TABLE 21.3

TARGETS FOR EARLY RESUSCITATION, PRIOR TO DEFINITIVE CONTROL OF HEMORRHAGE

Mental Status	Appropriate, Responsive to Commands (If Able to Assess)
Systolic blood pressure	80–90 mmHg
Heart	<120 bpm
Pulse oximeter	working, saturation >95%
Urine output	present
pH	>7.20
Base deficit, lactate	improving from admission value
Hematocrite	>25%
Prothromin time	<1.5 times normal
Platelet count	>50,000
Anesthetic state	Adequate analgesia and sedation

from fluid volume administration to fill a monitoring role. Trans-esophageal echocardiography is also helpful during early resuscitation, but requires a trained operator and bulky equipment. Near infrared tissue oximetry of the muscular beds of the deltoid or thenar emminence has been proposed and studied as a continuous indicator of hypoperfusion (29). Finally, sublingual capnometry, which measures the acidity of the mucosa under the tongue, has been found to correlate with serum lactate concentration (30). These latter two devices offer the most promise as continuous monitors of the shock state, but will require technological improvement and further clinical validation before they become routine.

A final strategic point concerns the role of anesthetic agents in the response to hemorrhage. Patients and laboratory animals are considerably more tolerant of blood loss when it occurs under general anesthesia, (31) perhaps because volume loss is more rapidly reflected in the vital signs in the absence of reflex compensation, perhaps because vasodilatation encourages early hemostasis, or perhaps because a decreased cellular metabolic rate reduces the systemic demand for oxygen. In fact, the use of anesthetic regimens to facilitate animal research into uncontrolled hemorrhage is a significant confounding variable in most published laboratory studies of resuscitation, which makes extrapolation of the results to trauma patients somewhat problematic. While bleeding following anesthesia (as occurs during elective surgical hemorrhage) is less likely to produce acute shock than bleeding while awake (as in the trauma patient), it is not known if the therapeutic application of anesthesia is beneficial to the patient already in shock. This question is especially difficult to answer because the induction of anesthesia will certainly exacerbate hypotension in the hypovolemic patient, regardless of the agents chosen. As a result, we are left with the ironic observation that most human trauma victims receive less anesthesia during active hemorrhage than the minimum required for an ethical study in animals.

Choice of Resuscitation Fluids

While the total volume of fluid infused during initial resuscitation has a strong influence on outcome, the types of fluid used are equally important. The clinician must strive to maintain the optimal blood composition for each phase of resuscitation, while minimizing the side effects of exogenous fluid and blood administration. Inevitably, a variety of different fluids are administered, each for a particular reason. Priorities for the maintenance of blood composition are listed in Table 21.4, in approximate order of importance during the initial stages of resuscitation. Table 21.5 lists the products in common use in the United States today, divided into three broad categories.

TABLE 21.4

PRIORITIES INFLUENCING THE CHOICE OF ADMINISTERED FLUIDS DURING RESUSCITATION FROM HEMORRHAGIC SHOCK, LISTED IN APPROXIMATE ORDER OF IMPORTANCE

- Maintenance of adequate intravascular volume.
- Maintenance of oxygen carrying capacity.
- Maintenance of clotting function.
- Maintenance of electrolyte balance.
- Minimization of extra-vascular edema.
- Minimization of immune system activation.

Crystalloids are electrolyte solutions that were developed as iso-osmotic analogues to the normal nonprotein content of human serum. As a class they are easily manufactured, inexpensive, readily available in all hospitals, and easy to administer. The simplest formulation—normal saline (Sodium Chloride solution)—is no more than salt water. Lactated Ringer's solution (LR) includes traces of other electrolytes found in serum: potassium and calcium, along with lactate to act as a buffer. Plasmalyte-A and other solutions are similar, except for the absence of calcium (to increase compatibility with blood transfusions), and the inclusion of magnesium. Plasmalyte-A is also buffered to a pH of exactly 7.4, whereas LR averages 6.5. Solutions containing glucose are not commonly used for acute resuscitation. Glucose release is a consequence of the sympathetic response to pain and hypovolemia, so serum levels are generally adequate without exogenous replacement, while hyperglycemia is associated with worse outcomes from both hemorrhagic shock and traumatic brain injury (TBI) (32,33).

Crystalloid administration is the most common and most immediate method of restoring cardiac preload, and thus blood pressure, during early resuscitation. Crystalloids are essential for the restoration of extravascular fluid stores following hemorrhage, but consequently have a short intravascular half-life (34). Crystalloids as a class have the disadvantage of diluting red cell mass and clotting factor concentration, and lowering the viscosity of the blood; all of these things contribute to increased hemorrhage in the actively bleeding patient. Crystalloid administration during early hemorrhage is thus a mixed blessing, and must be carefully titrated to avoid the negative consequences of over-infusion.

Limitation of crystalloid fluids during resuscitation has also been proposed and studied many times as a means of reducing subsequent edema in the brain, lungs, gut, and soft tissue, but this approach has generally not improved outcomes. The third space loss of fluids that characterizes tissue injury is a dangerous component of TBI, compartment syndromes, and the acute respiratory distress syndrome (ARDS),

TABLE 21.5
FLUID CHOICES FOR INITIAL RESUSCITATION FROM HEMORRHAGIC SHOCK

Fluid	Type	Comments
Normal saline	Crystalloid	Inexpensive, readily available
Lactated ringers	Crystalloid	Inexpensive, readily available
Plasmalyte-A	Crystalloid	Less expensive, readily available
Albumin	Colloid	More expensive
Hetastarch	Colloid	More expensive
Hypertonic saline with dextran	Colloid	Expensive, not currently licensed in U.S.
Red blood cells	Blood product	Expensive, limited supply, may transmit viral disease and prions, requires refrigeration
Plasma	Blood product	Expensive, limited supply, may transmit viral disease and prions, requires refrigeration
Platelets	Blood product	Expensive, limited supply, may transmit viral disease, short shelf life
Cryoprecipitate	Blood product	Expensive, limited supply, may transmit viral disease
Factor concentrates	Blood product or recombinant	Expensive, limited indications licensed in U.S.
HBOCs	Manufactured or recombinant	Expensive, not yet licensed for clinical use in U.S.

HBOC, hemoglobin-based oxygen carrier.

but fluid restriction does not modify this phenomenon in the desired fashion. Patients with severe injury and acute inflammation have an essential failure of barrier membranes and will leak fluids into the extracellular space even if exogenous administration is limited. If crystalloid administration has been restricted, this third space fluid loss will occur in the setting of intravascular depletion and diminished cardiac output, and may actually worsen cellular perfusion. Current recommendations for the management of both TBI and ARDS call for judicious fluid administration to maintain normal intravascular volume and a normal to high cardiac output (35,36).

Crystalloid solutions have been implicated in the recent past as immune system suppressants, (37) although the clinical consequences of this following acute resuscitation are not yet clear. The systemic inflammatory response syndrome (SIRS) that follows severe injury is characterized by a progressive imbalance of dozens of different mediators, both proinflammatory and anti-inflammatory, such that laboratory-proven immune suppression caused by crystalloid administration may be harmful, beneficial, or have no effect in a given patient. Interest in this phenomenon remains high, however, fueled by the recent finding that the L-racemic mixture of LR is not as active an immune modulator (38).

Colloids are characterized by the inclusion of proteins (albumin) or other large molecules (starch, gelatin, dextran) in a saline solution. This results in a significantly higher osmotic activity than crystalloid solutions, with the result that free water is drawn into the vasculature. Colloids thus offer the potential for expanding intravascular volume more than the amount of fluid infused. This makes them ideal for resuscitation in austere environments, including the battlefield, because an equivalent improvement in cardiac output can be achieved with a much lower volume of fluid.

Colloids are more expensive than crystalloids, but less than blood products. They do not require cross-matching and do not transmit viral diseases (albumin is derived from human blood but is heat-treated prior to packaging). They do not carry oxygen, and they do not contribute to coagulation. Like crystalloids, colloids are active immune modulators, although the clinical implications of this effect are poorly understood. Some colloids may also function as free-radical and inflammatory protein scavengers; albumin administration has been suggested to reduce the potential for fat embolus syndrome during long bone fracture repair, (39) while hypertonic saline with dextran (HSD) is thought to improve outcomes following TBI by mechanisms other than simple osmotic diuresis (40).

Proponents of colloid solutions for acute resuscitation invoke the osmotic benefit of reduced third space fluid loss as compared with crystalloids. Study of this phenomenon

has demonstrated that the antiedema effect is short-lived, however (40). While colloids will remain intravascular under normal conditions, in areas of tissue injury and membrane disruption they will still leak out into the extravascular space at a slow rate, followed by free water. The net clinical effect is that within a few days of traumatic injury, total fluid weight gain is equivalent with either crystalloid or colloid resuscitation. Another proposed advantage of colloid resuscitation is that microvascular perfusion is better maintained than with crystalloids, presumably as the result of the increased osmotic effect of these products (41).

Multiple clinical outcome studies have failed to demonstrate any consistent survival benefit to colloids over crystalloids. The most recent publication on this topic, the SAFE (saline verus albumin fluid evaluation) study, randomized nearly 7,000 ICU patients receiving fluid resuscitation, and found no difference in survival (42). The choice of resuscitation fluid is thus still largely based on logistical factors: expense, ease of use, and packaging.

Blood products generally refer to the natural occurring derivatives of donated whole blood. While whole blood itself may be the ideal resuscitative fluid for the patient in hemorrhagic shock, it is not generally available in the United States. The relative scarcity of donated blood and the expense of collecting and testing it, have made it economically more viable to dispense blood as fractionated components. Further, fractionation allows for a much longer storage half-life of some of the components, particularly plasma and clotting factor concentrates (43). Blood products are more expensive than either crystalloids or colloids and require relatively complex infrastructure for collection, storage, and readministration. While large American hospitals and trauma centers will generally have a ready supply of blood products at all times, smaller hospitals may not. One important caveat of perioperative transfusion medicine is that the clinician must always know how long it will take to obtain various blood products in a given clinical environment, once the need for them becomes apparent.

Blood products all have the potential for transmission of viral diseases, although the risk is small in the Western world. The most recent estimates range from 1/63,000 for any disease (with hepatitis B and C predominating) up to better than 1/1,000,000 for HIV (44). The incidence of transmission of emerging viral pathogens—such as West Nile Virus—is not known, but is being closely monitored. Prion transmission via donated blood has been reported, but is thought to be extremely rare diseases (45). Nonetheless, concern for viral transmission has lead to progressively more elaborate screening of potential donors, with a consequent scarcity of available blood in many locations.

Red blood cells (RBC) and plasma components have significant antigenic potential, such that a major ABO incompatibility between donor and recipient may produce a fatal hemolytic reaction. Indeed, the largest definable risk of RBC transfusion is clerical error resulting in a mismatched transfusion. This phenomenon resulted in nine deaths in 500,000 cross-matched transfusions during the Vietnam War, (46) and continues to be a preventable cause of mortality up to the present. Inverse cross-matching of transfused plasma is desirable to prevent a graft versus host effect. Platelets, cryoprecipitate, and specific factor concentrates are not generally cross-matched. Less severe transfusion reactions, characterized by fever, rash, itching, and tachycardia, are due to minor antigen incompatibility and may occur even with properly cross-matched blood. In the setting of acute resuscitation the greatest risk of a minor transfusion reaction is that it will distract clinicians from the patient's need for red blood cells, and will delay the restoration of oxygen carrying capacity.

Because failure of oxygen delivery is the central pathophysiology of hemorrhagic shock, timely administration of RBC is the most important component of resuscitation. In the patient with active hemorrhage and unstable vital signs nothing should delay the transfusion of the first units of RBC, including the time required for cross-matching. Large blood banks and major trauma centers maintain a ready supply of type O blood that can be immediately delivered to the bedside and administered to the hypotensive patient; this therapy may be life-saving in patients with rapidly exsanguinating injuries (47). Used this way, noncross-matched type O RBC transfusion is also safe; military experience during the Vietnam War documented more than 100,000 noncross-matched type O transfusions, with zero deaths attributable to allergic reaction (46). The relative immune suppression of the severely injured patient contributes to the safety of this technique, and even the development of antibodies in Rh– patients receiving noncross-matched Rh + blood is relatively rare (Hess, JR. personal communication, January 15, 2005).

When time and resources allow, blood products are transfused one unit at a time to maintain the desired hematocrit, prothrombin time (PT), and platelet concentration, with clinical and laboratory reassessment following each transfusion decision. The target hematocrit for acute resuscitation recommended in Table 21.3 above (25% to 30%) is higher than it would be for the patient who is not actively bleeding, in order to allow a margin of safety for ongoing hemorrhage. Similarly, although administration of plasma to the nonbleeding patient with an abnormal PT is seldom advantageous, it is appropriate in the setting of ongoing hemorrhage, as coagulopathy is easier to prevent than to treat in the patient in shock. Platelets should be administered only in the presence of active

bleeding, as their functional half-life once transfused is short. In trauma patients with an unknown medical history, platelet transfusion is occasionally necessary for surgically evident coagulopathy at counts higher than 50,000 per dl, due to dysfunction of native platelets from preinjury aspirin or platelet inhibitor therapy.

When treating the unstable patient with active hemorrhage transfusion decisions must be made in the absence of timely laboratory information, based only on the experience of the clinician. If transfusion requirement is likely to exceed one blood volume (8 to 10 units of RBC), our practice is to transfuse equal amounts of plasma and RBC, and one pheresis or pooled unit of platelets (6 to 8 random donor units) for each 8 to 10 units of RBC, while minimizing the volume of crystalloid resuscitation. The goal of this strategy is to treat the heavily bleeding patient with the closest possible substitute for whole blood. It is worth noting that one unit of donated blood, when mixed with an anticoagulant storage solution, centrifuged, stored for a period of time, and then recombined for administration to a single patient will have a hematocrit of 28% to 30%, a platelet count of about 50,000, and a clotting factor concentration of about 70% of normal (43). During massive transfusion it is thus unlikely that laboratory values any higher than this will be achieved and if significant quantities of crystalloid solution are given a critical deficit of RBC or clotting factors may occur.

Finally, it should be noted that blood products as a class are immunosuppressive, and that transfusion volume, independent of injury severity, is a predictor of mortality following severe hemorrhage (48). Transfusion-related acute lung injury (TRALI) is the predictable deterioration in pulmonary function that follows massive transfusion, probably as a result of the immunogenic load associated with multiple units of blood, plasma, and platelets (49). The ideal resuscitation protocol, therefore, is one that uses blood products aggressively in the early phase, to restore tissue perfusion and homeostasis, but much more selectively once bleeding has been controlled.

Hemoglobin-based oxygen carriers (HBOCs) represent an attempt to create a resuscitative fluid with the oxygen carrying capacity of RBC but without the need for cross-matching or the potential for viral transmission. Native tetrameric hemoglobin is unstable outside of the red cell membrane, and rapidly breaks down into myoglobin monomers and dimers that are toxic to the kidneys. Strategies for overcoming this obstacle have included a number of biochemical manipulations, including cross-linking the hemoglobin molecule, polymerizing it, and combining it with various lipopolysaccharide constructs to discourage dissolution. Further efforts were devoted to building a molecule with a physiologically appropriate p50 for oxygen (absent the effects of 2,3-DPG, found only within red cells), and to overcoming the unintended pharmacologic properties of the hemoglobin molecule. Hemoglobin is a natural scavenger for nitric oxide, and early hemoglobin solutions occasionally produced a profound vasopressor effect, especially in patients with underlying hypertension. After decades of work with these agents it seems likely that one or two such solutions will be approved for human use in this country within the next two years (50,51).

HBOCs have a much shorter systemic half-life (hours to days) than RBCs, meaning that their best use may be as a *bridge* to transfusion in the trauma or perioperative patient with significant active hemorrhage. A recently reported study examining the use of an HBOC during cardiac surgery showed a reduction in the number of patients who required transfusion (52). Another likely venue for the use of HBOCs is in the prehospital or military environment, where transfusion therapy is not currently available. Studies are underway to examine HBOC efficacy in this setting.

Completion of Resuscitation

Initial resuscitation from hemorrhagic shock, guided by the principles outlined above, continues until hemorrhage is definitively controlled. This point in time may be easy to define, as when the ruptured spleen is removed or a bleeding vessel embolized, or may require a transitional period of observation in which blood pressure is allowed to gradually increase, with careful monitoring of vital signs and wound output. In human trials of deliberate fluid restriction during early hemorrhage blood pressure was found to rise spontaneously when bleeding resolved, even without exogenous fluid administration (26,27).

Once hemorrhage has been controlled, the focus of resuscitation shifts to the optimization of oxygen delivery. Because exacerbation of bleeding is no longer a risk, more emphasis can be placed on achieving normal, or even supernormal, tissue perfusion. While an extended discussion of late resuscitation is beyond the scope of this chapter, it is easy to state the basic principle: fluid should be administered until the cardiac output is maximized and chemical markers of shock (e.g., lactate) have cleared (53). Successful late resuscitation thus depends on a conscious effort to investigate and correct the shock state. The syndrome of occult hypoperfusion arises because the clinician is misled by normal vital signs into believing that the patient is doing well (54). In fact, a healthy young patient may have a normal blood pressure, due to systemic compensation for shock, while still suffering from a 30% to 40% reduction in intravascular volume. If not recognized and treated, this patient will have ongoing ischemia at the tissue level and an increased likelihood of organ system dysfunction. Measurement of the cardiac output would reveal

a relatively low value, and measurement after a fluid bolus would indicate the presence of recruitable oxygen delivery (55). Similarly, this patient's lactate would remain elevated, despite normal vital signs, indicating the persistence of anaerobic metabolism. Studies have shown that the more rapidly lactate is cleared after an episode of hemorrhagic shock, the lower the subsequent incidence of organ system dysfunction and death (53). Late resuscitation therefore requires either the direct measurement and manipulation of cardiac output or indirect monitoring by way of serial measurement of the arterial blood gas and lactate.

Recommendations for blood composition also change in late resuscitation, once the threat of rapid exsanguination has been managed. A growing awareness of the side effects associated with transfusion (principally immune system modulation) have led to a greater tolerance for low hematocrit, elevated clotting time, and low platelets in the otherwise compensated and nonbleeding patient. Assessment of the effectiveness of perfusion (by following the lactate value) allows for transfusion of RBC at a lower trigger (20% to 25% hematocrit). There is little need for correction of laboratory abnormalities in PT or platelet count in the hemodynamically stable, nonbleeding patient.

SUMMARY

Initial resuscitation of the hemorrhaging patient is based on rapid identification and correction of the source of bleeding, coupled with fluid administration titrated to arrest and then reverse the pathophysiology of hemorrhagic shock. Resuscitative fluids must be administered at a rate sufficient to support tissue perfusion, but not so fast that bleeding is increased. Early use of RBC and plasma can help to preserve oxygen delivery and coagulation in the unstable patient, while vigilant monitoring of vital signs, filling pressures, and laboratory markers will allow for increased precision of resuscitation over time, with restoration of normal physiology once bleeding is controlled.

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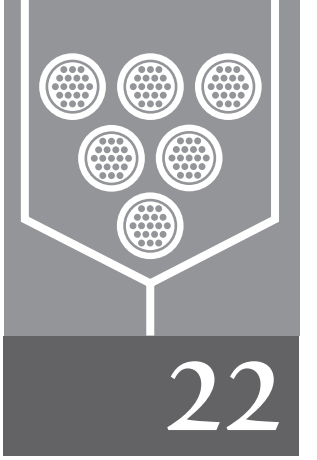

22

Transfusion and Coagulation Therapy in Trauma and Burns

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HISTORY

The first transfusion of human blood for the treatment of hemorrhage was performed by Dr. James Blundell in London on December 22, 1818. Over the next 11 years Dr. Blundell transfused nine more patients for hemorrhage, five of whom survived (1). The death rate from early transfusions was estimated to be 50% because of blood incompatibilities, inadequate resuscitation, and sepsis. The development of blood group typing and anticoagulants for stored blood enabled blood for transfusion to be collected in advance, eliminating the practice of direct donor patient transfusion. During World War I, a few hundred patients were transfused. At that time, most surgeons had not distinguished between the causes of shock (septic, hemorrhagic, cardiogenic, neurogenic) and hypovolemia following hemorrhage was inadequately treated, if treated at all (2). Nevertheless, the technique of blood transfusion was refined during the war and its use increased (3). Some accurately determined that the cause of hemorrhagic shock was blood loss, and blood transfusion was appropriate therapy (4). By the end of World War I, O positive blood was stored in citrated bottles and generally used up to 14 days after collection (5). Early indications for blood transfusion were: (a) perioperative preparation for hemorrhage and shock, (b) during operation, (c) after operation in depressed patients, (d) carbon monoxide poisoning, and (e) septicemia and chronic wound infection. Administration of 500 to 600 mL of whole blood was considered adequate in shock (6).

In 1922, Dr. Percy Oliver, a London physician, had established a donor pool—a walking blood bank on call when needed—and performed 13 transfusions. The initiation of sodium citrate as an anticoagulant in the early 1900s allowed blood to be collected and refrigerated for later use, eliminating the need for direct arm-to-arm transfusion. By the mid-1930s blood banking was well established in the Soviet Union, primarily using cadaver blood, and the cause of hemorrhagic shock had been clearly elucidated (7). In 1937, Dr. Bernard Bantus established the first United States blood bank at Cook County Hospital in Chicago, capitalizing on the blood banking experience from the Spanish Civil War. By the eve of World War II, the major components of blood banking, as we know it today, were in place. Additionally the use of plasma as a resuscitation fluid was gaining acceptance.

The first efforts at large-scale provision of blood to a combat zone were undertaken by doctors Norman Bethune and Federico Duran-Jorda in the Spanish Civil War. Blood was collected, stored in citrated bottles, and delivered on an as-needed basis to operating rooms (OR) or to the front. At the onset of World War II, the British developed a transfusion service and began to provide blood and plasma to the injured. The results appeared satisfying (1). Transfusions were used to treat hemorrhagic shock, crush injuries, burns, and lacerations. There was general agreement that blood transfusion benefited the trauma patient, but little knowledge existed regarding when transfusion was indicated (as opposed to other fluids), and to what hemoglobin level a patient should be transfused. Much of

the impression that blood was useful in trauma was based on historical and anecdotal accounts as opposed to rigorous outcome-based studies with randomized treatments.

During the early years of World War II it was recognized that plasma infusions were capable of resuscitating people from hemorrhagic shock. (Fig. 22.1) Plasma could be stored longer than blood and no cross-matching was needed for infusion. The development of freeze-dried plasma further prolonged its shelf life and made it a desirable fluid for resuscitation where blood was unavailable or impractical (3). Early in the war it was erroneously thought that shock was due to the loss of plasma into the extravascular tissue spaces (8). Plasma was favored for resuscitation because it was more easily available than whole blood, felt to be more efficacious than blood for burns and other injuries, and helped correct dehydration, a common accompaniment to injury (8). Indeed, during the early part of the war, plasma was often the only resuscitation fluid used by American forces. The British and American governments began extensive plasma programs to provide for the massive numbers of injured. Techniques were developed for producing dried plasma and albumin, which was also produced in quantity. Still, in the early days of the war, the treatment of hemorrhagic shock was in its infancy and standard treatment consisted of morphine, bed rest with leg elevation, and external passive warming (9).

The lessons learned from World War II were that: (a) blood, plasma, and albumin were lifesaving for severe hemorrhagic shock, (b) patients who were resuscitated early and adequately fared better than those who were not, (c) the amount of blood or fluid required for adequate resuscitation was frequently considerably larger than at first guess, and d) in hemorrhagic shock the preferred resuscitation fluid is whole blood (10). As whole blood became more readily available, it supplanted plasma as the resuscitative fluid of choice for hemorrhage and the practice of blood out–blood in came into vogue. Indeed, if we had safe and adequate supplies of fresh whole blood for hemorrhage, we might still use this model for resuscitation, because it is often considered the best resuscitative fluid for severe hemorrhage (11).

Figure 22.1 Administering plasma to wounded man at 7th Infantry aid station, Sant'Agata, Italy, World War II, 7th Infantry Regiment, 3rd Infantry Division.

During the Korean War whole blood transfusions were given as far forward as the regimental units (12). It was recognized that inadequately treated shock could lead to renal failure (13). Since under resuscitation from hemorrhagic shock could result in renal failure, by the Vietnam War, large amounts of crystalloid were administered for hemorrhagic shock, resulting in less renal failure and the development of a new problem—Da Nang lung (14). Because hemorrhagic shock had been treated during World War II and the Korean War with whole blood and colloids (primarily plasma), the fluid volumes administered were less than those required for crystalloid solutions, and the third space problems of edema identified with crystalloid infusions were less apparent. When the change to packed red cells and crystalloid for hemorrhagic shock resuscitation was made, acute respiratory distress syndrome (formerly the adult respiratory distress syndrome) became a more common sequellae to hemorrhagic shock (15). Due to short evacuation times and the ready availability of blood products and resuscitation fluids, injured combatants in Vietnam survived more often than in previous wars (16). It was not uncommon to administer 80 or 90 units of packed cells during resuscitation and initial surgery (17).

By the close of hostilities in Vietnam the basic resuscitative measures for dealing with blood loss had been developed and were beginning to be well utilized and debated. Much of what we do today for hemorrhage has remained basically unchanged, though our understanding and employment of resuscitation have been refined. Still, much remains to be learned. What is the best transfusion trigger? Can transfusions be avoided? How can we further optimize resuscitation within the framework of limited access to technology and supplies in the field?

WHAT IS HEMORRHAGIC SHOCK?

The end result of severe bleeding is hemorrhagic shock. It is helpful to understand shock fully in order to effectively use the array of available treatments, only one of which is blood transfusion. Shock can be defined as the inadequate supply of oxygen to support cellular metabolic machinery

(18). This is certainly the end result of severe hemorrhagic shock, but is not a helpful definition to the clinician. Depending on the degree of hemorrhage, not all tissues will be hypoxic or dysoxic. The problem confronting the clinician is to rapidly detect the presence of hypoxia/dysoxia in some tissues following blood loss so that effective countermeasures may be instituted.

Fortunately we have a good understanding of the physiology of hemorrhagic shock. By being alert to the signs and symptoms of blood loss, the astute examiner can institute corrective action before cellular hypoxia become irreversible. The American College of Surgeons Committee on Trauma has classified blood loss in stages so that one may have a rough idea of the amount of blood lost by clinical presentation. (Table 22.1)

Hemodynamic changes in response to blood loss begin with the traumatic event (19). The changes are time-dependent and related to the extent of injury. For the physician treating the trauma victim, the goal is to diagnose and treat blood loss early, before shock begins. To do this one must be attuned to the early changes following blood loss. The physiologic response to hemorrhagic shock has been used as a clue to the extent of blood loss. However, this response is imprecise and is not uniform in all patients and the examiner may be misled. For example, tachycardia is one of the earliest responses to blood loss, but some patients respond with relative bradycardia (defined as a pulse less than 90 beats per minute in the presence of hypotension) (20). Paradoxical bradycardia may also occur with drug and alcohol use (21). Hypotension only occurs after other compensatory mechanisms (catecholamine release, vasoconstriction, tachycardia, increased cardiac contractility) have failed. The blood pressure is notoriously variable in hemorrhage, and while blood pressure eventually falls during continued hemorrhage, it may rise transiently (especially the diastolic pressure during early hemorrhage), or be depressed by alcohol or other intoxicants (22). Therefore, no single physiologic parameter should be accepted as the sole indicator of the extent of blood loss. In shock, blood is shunted from the intestinal vasculature and subcutaneous vessels to other organs, resulting in changes in intestinal function (23) and the cool skin typical of the shock victim (24,25). After a period of profound hemorrhagic shock, cardiac function can decline with a loss of cardiac contractility (26). Shock induces changes in neutrophils, making them more responsive to inflammatory cytokines as mediators of postshock injury such as the acute respiratory distress syndrome (27). As the trauma victim suffers worsening regional ischemia, inflammatory cytokines are upregulated, which play important roles in the development of remote organ injury and failure (28,29).

Hemorrhagic shock should be distinguished from anemia. Anemia is a reflection of the number of circulating red blood cells and initially is indicative of the amount of blood lost, assuming the trauma or burn victim was not anemic preinjury. Later in the hospital course, anemia may be a reflection of chronic disease—e.g., immunosuppression, infection, and organ failure. It is important to stress that while most victims of major trauma become anemic, anemia alone is not necessarily an indication for therapeutic

TABLE 22.1
ADVANCED TRAUMA LIFE SUPPORT BLOOD LOSS CLASSIFICATION

The four classes of shock based on blood loss with associated clinical signs

	Class I	Class II	Class III	Class IV
Blood loss (mL)	up to 750	750–1500	1500–2000	2000 or more
Blood loss (%BV)	up to 15%	15–30%	30%–40%	40% or more
Pulse rate	<100	>100	>120	140 or higher
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (SBP-DBP)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Delayed	Delayed	Delayed
Respiratory rate	14–20	20–30	30–40	>35
Urine output (mL/hr)	30 or more	20–30	5–15 or less	Negligible
CNS-mental status	Slightly anxious	Mildly anxious	Anxious and confused	Confused, lethargic
Fluid replacement (3:1 rule)	Plasma volume expander	Plasma volume expander	Plasma volume expander + PRBC	Plasma volume expander + PRBC

Values based on a 70-kg male.
(Reprinted with permission from American College of Surgeons Committee on Trauma. Advanced Trauma Life Support Course. Chicago, Ill: American College of Surgeons; 1997:98.)

intervention (30). The decision to transfuse should be coupled with other knowledge—clinical symptoms, rate of ongoing blood loss, degree of control of bleeding, signs of illness (e.g., myocardial ischemia), or the knowledge that given a certain level of anemia and certain injury states or need for further operative intervention with an expected large volume blood loss (e.g., hepatic unpacking), transfusion provides an outcome benefit. A common misconception is that a certain hemoglobin level, a transfusion trigger, can be used as a sole indicator of the need to transfuse. This was probably not the intent of those developing transfusion guidelines, but in the tendency to simplify transfusion rules, the clinical condition of the patient as an indicator for transfusion is sometimes forgotten. The decision to transfuse should not be made solely on the basis of a patient reaching a certain transfusion trigger, but should include other clinical input as identified above. Moreover, certain biochemical markers of poor tissue perfusion, such as arterial lactate, may play a role in deciding to transfuse a given patient.

DIAGNOSING HEMORRHAGIC SHOCK

One of the pitfalls in treating hemorrhage is the failure to recognize and appreciate the extent of blood loss. Once having made this error, the clinician will have difficulty in resuscitation, and results may not be satisfactory. Every moment of cellular hypoxia initiates intracellular event signaling, which may be long-lasting and difficult, if not impossible, to correct (31). Therefore an early and accurate diagnosis of hemorrhage is crucial.

Symptoms

Untreated hemorrhagic shock can ultimately result in death. Hemorrhagic shock is the most common cause of death in trauma and accounts for approximately three fourths of trauma deaths within the first 24 hours after injury (32). First responders are much more likely than hospital staff to encounter trauma victims dying of blood loss. Symptoms include, but are not limited to, confusion, sometimes interspersed with surprising lucidity, thirst, reporting feeling cold despite adequate ambient temperature, detachment, and often, shortness of breath (17). Severe blood loss may be accompanied by typical anginal pain, even in the absence of coronary artery disease (33).

Signs

In advanced hemorrhagic shock, the victim will be pale, with a weak, rapid, and thready pulse. Because of cutaneous vasoconstriction in response to catecholamines the skin may feel cool and clammy. Urine output will be low, and respirations will be rapid. Increased heart rate, lowered systolic but raised diastolic pressure, accompanied by low central venous pressure will be present (34). Pulse oximetry may be unobtainable due to vasoconstriction. The electrocardiogram may show signs of ischemia or conduction abnormalities.

Laboratory Analysis

One of the most useful tools in determining the adequacy of oxygenation is oxygen debt. Oxygen debt is a conceptual calculation of how much oxygen is not being consumed (oxygen consumption is expressed as VO_2, and oxygen debt = VO_2 (ideal)−VO_2 (actual) = mL/min.). (Table 22.2) The debt is expressed in mL O_2/kg/minute and correlates well with outcome. The higher the oxygen debt, the more likely a poor outcome or death (35,36). An oxygen debt of 115 mL/kg/min = 50% probability of death for a 70 kg person (37).

A more simplified method of predicting survival and outcome is to use base deficit (acidosis) as an indicator of oxygen debt. Base deficit and lactate levels have been correlated with acute respiratory distress syndrome (ARDS). A base deficit of 8.0 mmol per L or greater in a 24-hour period is predictive of a 50% probability of ARDS; the greater the base deficit, the earlier the ARDS appears postinjury (35). Similarly, a lactate level of 7.0 mmol per L or higher during a 24-hour period renders a 50% probability of ARDS (35). Lactate levels have been shown to correlate better with oxygen debt than blood pressure or volume of blood loss (38). Elevated lactate and base deficit are signs of severe shock; normal values are not always reflective of adequate resuscitation.

Using Resuscitation to Help Diagnose Hemorrhage and Early Shock

Occasionally, despite the best efforts of the clinician, the presence of hemorrhage may not be certain, or the extent of blood loss is uncertain. This is more likely to occur early

TABLE 22.2
OXYGEN CONSUMPTION

Oxygen consumption
$VO_2 = CO \times (CaO_2 - CvO_2)$
Note: Oxygen delivery (DO_2) is 4-5x greater than VO_2
Normal values for oxygen consumption – (VO_2)
200-250 mL / min (70 Kg person with 15 g Hgb)
~ 3 mL / Kg / min

after injury or in austere settings when more sophisticated techniques for the diagnosis of internal hemorrhage such as diagnostic peritoneal lavage or FAST examination (Focused Assessment by Sonography in Trauma) may not have been performed or may not be available. Faced with a clinical picture that suggests hemorrhage and developing shock, the clinician may try a fluid challenge with the rapid infusion of 500 mL of crystalloid or colloid and carefully monitor physiologic variables for signs of improvement. Physiologic variables that are of use include heart rate, blood pressure, urine output, base deficit, and lactate. A host of others including sublingual capnometry, impedance plethysmography, and near infrared spectroscopy are being assessed for clinical validity and efficacy, but are not yet standard of care. If clinical improvement ensues, hemorrhage that occurred and has been arrested should be suspected. If there is no improvement in those physiologic variables, then ongoing hemorrhage should be assumed and resource appropriate action taken.

THE ROLE OF BLOOD PRODUCTS IN TRAUMA: WHY DO WE TRANSFUSE IN TRAUMA?

Goals

Preserve Life

The first goal in resuscitation from hemorrhage is to preserve life. With nearly 100 years experience in resuscitation from hemorrhage with blood products, the reported influence on mortality is inconclusive. No doubt administration of blood to some individuals suffering from advanced hemorrhagic shock is beneficial, and anecdotal evidence from World War II bears this out (10). In the Vietnam War, 70% to 80% of fatalities classified as killed in action (KIA) occurred within minutes (39). Half of these (35% to 40%) died from complications of exsanguination. About 67% of those who died of exsanguinations had wounds that were not immediately lethal and potentially salvageable (e.g., to the extremities). If one assumes that the causes of death among casualties classified as KIA (i.e., expired before evacuation for medical treatment) are distributed as follows—36% craniocerebral (CNS), 50% hemorrhage, and 14% other—it is quite apparent that the most practical means to increase survival through evacuation is to address the 50% of casualties who die from hemorrhage. Similarly, about half the mortality from grade IV and V liver trauma is from exsanguination (40). When transfusion requirements in the OR become vast (>4000 mL) there is a strong correlation with death (41).

Another body of evidence suggests that in some circumstances, blood transfusion does not alter the outcome from trauma and hemorrhage. Admittedly, it is difficult to determine the true benefit of blood transfusions in trauma patients without proper randomized trials using blood conservation methodology, because higher transfusion requirements are linked to a poorer outcome (42). In hip fractures, blood transfusion appeared to make no difference in the outcome (43). A study of perioperative transfusion and mortality identified no clear link between perioperative mortality and transfusion (44). Improved outcome studies are required to definitively elucidate the relationship between blood transfusion and mortality from trauma.

Prevention of Major Organ Dysfunction

Nearly every trauma surgeon has had the experience of resuscitating a trauma patient from near exsanguination, flawlessly performing the required operation(s), only to have the patient expire 2 to 3 weeks later from multiple organ failure. Hemorrhagic shock is associated with cellular hypoxia that initiates a cascade of cellular and organ level events, which may result in organ failure. Cellular hypoxia in trauma derives from several discrete but linked events. These events include blood transfusion (45), hypovolemia, low cardiac output, poor tissue perfusion, low oxygen carrying capacity, acute severe anemia, sepsis (46), hypothermia (47), inflammatory cytokines (48,49), inadequate or overzealous resuscitation (50), and direct organ injury. The sequence of events is believed to be as follows: cellular hypoxia releases inflammatory cytokines (51) (principally TNF-α, IL-1β, and IL-6) which cause tissue edema, further hypoxia (52), inflammatory cell migration, translocation of bacteria from the intestines (53,54), sepsis, and further release of inflammatory cytokines creating a vicious and self-propagating cycle of inflammation. (Fig. 22.2) A single organ may auto-amplify this process, worsening regional hypoxia and initiating remote organ failure. Therefore, every effort should be made to prevent hypoxia on a cellular level.

Reduction of Tissue Damage—Improve Wound Healing

The relationship between wound healing and anemia is complex, since wound repair hinges on tissue level pO_2 and profound anemia diminishes this important variable. The magnitude of anemia required to impair wound healing remains to be determined. Early research demonstrated that even severe anemia (Hgb = 6 g per dL) did not affect wound healing; this finding has been confirmed in more recent studies (55–57). However, a growing body of evidence has linked anemia to poor outcomes such as impaired fracture healing (58), failure of spinal fusion (59), reduced intestinal anastomosis bursting and tensile strength (60,61)

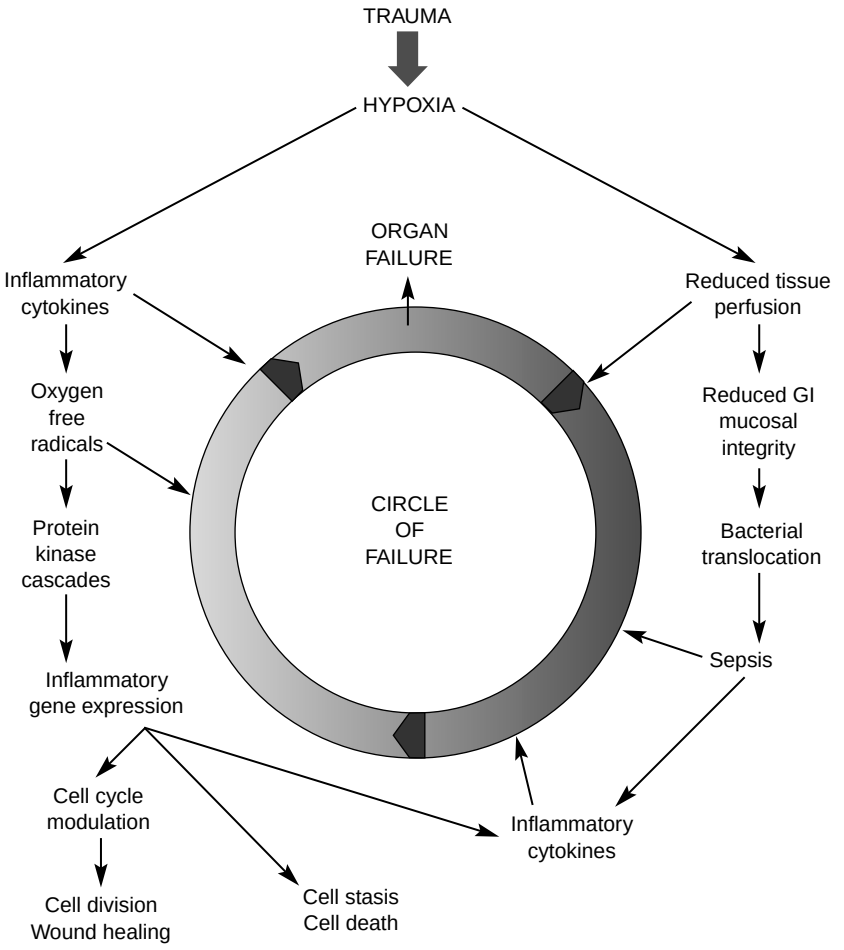

Figure 22.2 Trauma processes leading to organ failure.

and delayed wound healing (62). From the foregoing evidence, one might assume that anemia is equated with poor outcomes in wound healing. However, even though anemia frequently is present in cases of poor wound healing, the role of anemia as a causative agent in poor wound healing is in dispute. It is important to note that in acute blood loss it is difficult to distinguish anemia from hypovolemia, and the two often coexist. Hypovolemia clearly impairs wound healing, and thus the finding of impaired healing in anemia may simply represent inadequate volume resuscitation.

Improve Outcome

It is intuitively attractive that trauma patients with higher hemoglobin would do better than those with lower hemoglobin levels. In a retrospective study of 5,793 hip fracture patients, a higher postoperative hemoglobin level was linked to a better outcome (63). Blood transfusion is only one method by which a higher postoperative hemoglobin level may be achieved. Blood transfusion is an independent predictor of mortality, ICU admission, and hospital length of stay after trauma (64).

Correction of Hypovolemia

The correction of hypovolemia in hemorrhagic shock is a worthy goal. How much correction is needed to improve outcome is unclear (65). Too little correction of hypovolemia and the trauma or burn victim suffers hypoxic organ damage. Too much correction by overzealous fluid administration may initiate rebleeding in the presurgical setting, as well as posttraumatic acute lung injury/acute respiratory distress syndrome. Thus, a reduced mean arterial pressure target appears to be a reasonable compromise prior to definitive hemorrhage control. This strategy seeks to protect end-organs from hypoxic damage while balancing the resuscitation risk from induced hyperchloremic acidosis and acute lung injury (66).

Improvement of Oxygen Carrying Capacity

Each gram of hemoglobin carries 1.34 mL of oxygen when fully saturated (67). An individual with 13.5 gm of hemoglobin per deciliter then carries approximately 18 mL oxygen per dL in circulating arterial blood. To this must be added the amount of oxygen dissolved in the plasma. Each dL of plasma carries 0.003 mL of dissolved gaseous oxygen

TABLE 22.3
PERCENT OF AVAILABLE O_2 CARRIED BY PLASMA (PATIENT BREATHING 100% O_2–100% SATURATED)

Hgb in gm / dL	% O_2 in Hgb	% O_2 in Plasma
15	90	10
10	85	15
7	80	20
5	75	25
4	70	30
3	64	36
2	54	46
1	37	63

for each mm of mercury oxygen pressure. When breathing 100% oxygen this amounts to about 2 mL per dL oxygen dissolved in the plasma, or about 10% of the total oxygen content of the blood (assuming normal hemoglobin content). As the hemoglobin content falls, the plasma fraction of dissolved oxygen amounts to a more significant fraction of the total oxygen content. From Table 22.3 one appreciates the increasing advantage to placing an individual on 100% inspired oxygen as hemoglobin content falls. In essence, raising a patient's inspired oxygen from room air to 100% oxygen amounts to adding the equivalent oxygen-carrying capacity of 0.84 units of normally functioning red blood cells. In reality, based on reduced levels of 2,3-DPG and banked RBC dysfunction, the effect of 100% O_2 on arterial O_2 content is closer to transfusing 2 units of stored packed red blood cells.

There are two physiologically based methods to increase the oxygen carrying capacity of the blood. One is to increase the hemoglobin, or add another oxygen-carrying substance to the blood such as fluorocarbons or hemoglobin based oxygen carriers (HBOC). The other method is to increase the pressure of inspired oxygen by increasing FiO_2 and/or the ambient pressure. The ambient pressure is usually increased in a hyperbaric chamber. This therapy is reserved for extreme blood loss when blood is either not available or an option. (68,69)

Improve Oxygen Delivery

Having provided for correction of hypovolemia and adequate oxygen-carrying capacity of the blood, delivery of oxygen to the tissues must be addressed. Physiologic parameters rather than a set hemoglobin level, should be utilized to assess oxygen delivery (70,71). When cardiac output and tissue perfusion are optimized, and oxygen delivery remains inadequate in the setting of anemia, red cell transfusions are indicated.

Improvement of Tissue Oxygenation

Which tissue is at risk of developing ischemia and which tissue needs to be treated? Prolonged cellular hypoxia may develop into irreversible cell damage and cell death (72). Cells are capable of exquisite sensitivity in detecting oxygen tension. Even a short period of hypoxia initiates gene transcription (i.e., hypoxia inducible factor) resulting in a cascade of intracellular and extracellular events that lead to organ failure if the hypoxic insult has been severe (72). Hypoxia in trauma victims that results in a persistent base deficit has been related to higher mortality (73). Evaluation of subcutaneous oxygen tension shows that it falls before arterial pressure and stays depressed for up to 60 hours in the setting of marginally inadequate resuscitation (other vital signs within the normal range) (24,74). Transcutaneous and subcutaneous oximetry are powerful and sensitive tools for measuring the adequacy of resuscitation; it is likely that these parameters have been underutilized in clinical practice. A transcutaneous oxygen level less than 30 mm of mercury on room air and less than 50 mm of mercury on 100% oxygen are generally accepted as evidence of local tissue hypoxia (75,76). Subcutaneous oximetry remains experimental, but transcutaneous oxygen monitors are readily available (77).

How is tissue oxygenation determined? One of the difficulties in assessing the adequacy of resuscitation using physiologic parameters is that tissue hypoxia may be present and yet undetected by those parameters. Seemingly adequate resuscitation may coexist with profound regional hypoxia, especially at the site of injury. A classic example is the burned patient with an adequate cardiac output, satisfactory delivery of oxygen through the larger blood vessels, but severe burn wound hypoxia (78).

When Is Transfusion Necessary?

What Is the Goal of Red Cell Transfusion?

"Resuscitation from shock can therefore only be complete when all evidence of oxygen debt, anaerobic metabolism, and tissue acidosis has been eliminated" (79, p.10). The end goal of transfusion is to restore tissue oxygenation that was compromised by loss of hemoglobin and oxygen-carrying capacity. A low hemoglobin level by itself is not reason enough to initiate transfusion. Correlation with other clinical conditions must also exist. These clinical conditions include but are not limited to: systemic acidosis, low cardiac output, and evidence of end-organ ischemia.

Decision Process for Red Cell Transfusion

The initiation of transfusion with PRBC should be accomplished methodically according to a predetermined plan. Decision making algorithms speed the resuscitation process,

conserve resources, and more rapidly achieve results. Blood products (primarily packed RBCs) should begin when the following conditions are met:

Evidence of tissue hypoxia exists:

Clinical signs of hypoxia, lactic acidosis, increased base deficit, oxygen debt, ***and***

Hypovolemia has been corrected by crystalloid and/or colloid, ***and***

Supplemental 100% oxygen is being administered, ***and***

Cardiac function and tissue perfusion is optimized, ***and***

Evidence of hemoglobin deficit exists—(usually 7 g per dL but can vary according to the needs of the patient)

OR

There is evidence of active hemorrhage in association with shock, ***or***

The lack of immediate ability to control hemorrhage, and RBC transfusion may prolong life until hemorrhage control is achieved.

In each of these conditions supplemental oxygen and rapid infusion of fluids are ideally undertaken prior to RBC infusion. However, in urban trauma centers, these events frequently occur concomitantly with RBC infusion in the setting of hemorrhagic shock.

When Does One Stop Transfusion?

Just as for initiating transfusion, terminating transfusion is not dependent on reaching a predetermined hemoglobin level but instead relies upon a satisfactory improvement in the patient's clinical condition. Transfusion may be stopped when the following conditions are met:

Tissue hypoxia has been corrected, ***and***

Hypovolemia has been corrected with volume expanders (crystalloid and/or colloid), ***and***

Cardiac function has been optimized, ***and***

Hemoglobin levels are acceptable, ***or*** no signs or symptoms of hypoxia are evident.

How Is Transfusion Efficacy Measured?

As transfusion is undertaken one ought to monitor oxygen debt, tissue oxygenation, base deficit, and/or lactate levels to measure efficacy. Improvements in each of these key markers of resuscitation correlate with the efficacy of increased red cell mass and arteriolar O_2 content. However, the transfusion of RBCs may not immediately translate into a tissue oxygen level increase. Stored RBCs are deficient in 2,3 DPG, which is necessary for the transmembrane transport of oxygen, and may not function normally until several hours after transfusion when RBC levels of 2,3 DPG are restored (79,80,81). Stored red cells evidence limited deformability, which inhibits cell transit through small vessels. As a result of these properties of stored RBCs, tissue oxygenation levels may decline for a period of time after stored red cell transfusion (82). Therefore one should not assume tissue oxygenation has been corrected because RBCs have been transfused. Furthermore, increases in red cell mass unaccompanied by plasma volume expansion may fail to increase tissue oxygenation in the face of inadequate cardiac output if volume recruitable cardiac performance has not been optimized.

TRANSFUSION PLAN

One should not undertake transfusion without prior preparation. The emergency department bedside is not the place to develop a blood transfusion plan. Using a treatment algorithm, such as the one offered in this chapter, one should strive to administer blood products only when necessary, according to a predetermined plan so that blood product use may be minimized, while clinical outcomes are maximized.

SPECIAL CONSIDERATIONS FOR BURN PATIENTS

Burn injury does not require transfusion early in the course of care, unless surgery with blood loss is performed (83). Excision and grafting is accompanied by prolific blood loss at times and all components of blood and clotting factors may need to be replaced (84,85). Late in the course of burn injury, patients may suffer from the anemia of chronic disease, exacerbated by malnutrition, and phlebotomy for laboratory testing. Several interventions may minimize burn patient transfusion requirements (86):

1. administration of erythropoietin early in the course of care (87).
2. use of blood conservation strategies during burn wound excision.
3. use of topical hemostatic agents (fibrin, fibrin glue) during burn excision and grafting.
4. staged excision and grafting where appropriate and where outcome is not compromised.
5. careful attention to hemostasis during burn excision (88)
   - use of extremity tourniquets
   - tumescent technique of excision with dilute epinephrine solution.
6. early excision of the burn wound prior to bacterial infection.
7. minimizing blood draws.

Acutely burned patients may have significant depression of erythrocyte function from carbon monoxide and smoke inhalation. Initiation of 100% normobaric or hyperbaric oxygen is appropriate in this setting (89,90). Burn victims suffer from a complex array of inflammatory responses which may result in consumptive coagulopathy, immunosuppression, and depressed red cell synthesis (91). Careful monitoring of the coagulation status of burn patients and the correction of coagulopathies is an important part of burn resuscitation. Administration of fresh frozen plasma, cryoprecipitate, and platelets may be required (92). The administration of red cells to the acute burn patient should follow the guidelines suggested above for other trauma patients.

OTHER MEASURES OF RESUSCITATION

Supplemental O_2

One of the easiest and most effective means of helping the hemorrhaging patient is to provide supplemental oxygen. If a patient has bled, is bleeding, or is thought to be bleeding, 100% oxygen should be administered. By 100%, it is intended that the inspired oxygen fraction (FiO_2) is 100%. This may be achieved by a tight-fitting, well sealed mask, hood or other device and high flow oxygen, or through endotracheal intubation or cannulation. The plastic oxygen mask with air vents is to be shunned in the emergency setting as these apparata typically deliver only 25% to 70% oxygen, depending on the oxygen flow rate, and the patient's minute ventilation. As hemoglobin levels decrease, the proportional contribution of dissolved O_2 increases, so that O_2 saturation becomes progressively less important than O_2 partial pressure. (Table 22.3)

Even with a low hemoglobin concentration, a significant amount of oxygen is carried in the plasma. In fact, the plasma oxygen fraction becomes progressively more important as the hemoglobin level declines. Additionally, plasma circulates to deliver the carried O_2 through capillaries whose diameters are too small to readily transmit red cells. Oxygen is a potent vasoconstrictor due to its action on the vascular endothelium. Increasing FiO_2 may also therefore increase tissue perfusion pressure (93).

The utility of oxygen administration should not be overlooked, even in the young and seemingly healthy patient. In a French study of young women with severe postpartum hemorrhage, 51% showed evidence of myocardial damage as evidenced by elevated troponin and electrocardiographic signs of injury (34). This study provides important, although indirect, evidence that plasma volume expansion alone may be insufficient, and that supplemental oxygen may be beneficial and conditionally required to complete resuscitation, even in the physiologically sound but hemorrhaged patient.

Crystalloid Infusion

The infusion of crystalloid solutions for hemorrhagic shock resuscitation is a long-standing practice (5). Crystalloid infusion represents the current civilian standard of care for initial traumatic blood loss resuscitation in the Unites States. Typically, for every milliliter of shed blood three to four milliliters of crystalloid must be infused to restore effective circulating volume. The advantages of crystalloid solutions (primarily Ringer's lactate solution) are that they are nearly universally available, cost-effective, and have few immediately identifiable untoward side effects.

However, a growing body of evidence suggests that large volume resuscitation with crystalloid solutions, even lactated Ringer's solution, carries subtle and persistent disadvantages compared to other forms of plasma volume expansion. The gold standard for hemorrhagic shock resuscitation is whole blood—a commodity rarely available in our current era of component transfusion therapy. Readily apparent increases in mean or systolic pressure achieved by crystalloid resuscitation may be only transitory, indicating accelerated hemorrhage or volume redistribution outside of the intravascular space. These events were recognized as early as 1942 (94). When compared to blood, hemoglobin-based oxygen carriers (HBOCs), or colloids, and crystalloid solutions take longer to restore mean arterial pressure and tissue oxygenation, resulting in higher lactate levels (95,96). Crystalloids also contribute to reduced intracapillary osmotic pressure and viscosity and may contribute to organ dysfunction through inadequate capillary extraction of metabolic products (97). Increasing the plasma viscosity may allow for a reduced transfusion trigger.

A recent concept in the prehospital resuscitation of trauma patients is *delayed resuscitation* or *hypotensive resuscitation*. In this type of resuscitation, the prehospital blood pressure is maintained at subnormal levels during initial resuscitation. The concept came about through recognition that aggressive resuscitation in the presurgical trauma victim could raise blood pressure sufficiently to cause renewed or more vigorous bleeding, further aggravating tissue hypoxia and causing depletion of clotting factors through hemodilution. By keeping blood pressure just high enough to maintain minimal organ function, it is thought that bleeding can be minimized and outcomes improved. A study of 598 patients with penetrating torso injuries showed that delayed resuscitation resulted in improved survival, fewer complications, and shorter hospitalizations (98). A randomized study evaluating the

differences between immediate and delayed crystalloid resuscitation for trauma victims showed no difference in outcome, though the delayed resuscitation group did slightly better (99). In another study, maintaining the systolic blood pressure at 70 mm Hg did not adversely affect survival (100). Conversely, the optimization of blood pressure during resuscitation of bleeding patients to normal levels does not appear to improve survival (101). At the time of this writing the indications and parameters for hypotensive resuscitation of bleeding trauma patients have not been fully worked out but certainly deserve further investigation.

Crystalloid solutions do not inherently add oxygen-carrying capacity, but assist in oxygen-carrying capacity and delivery by (a) restoring intravascular volume and cardiac output, (b) enhancing tissue perfusion, and (c) improving the rheology of the red cells in shock (in the absence of acidosis). Once effective circulating volume has been restored, but signs of inadequate oxygenation persist, oxygen carrying capacity must be augmented by other methods, such as red cell transfusion (102,103). Other disadvantages to resuscitation with crystalloid solutions alone are promotion of the inflammatory cascade (WBC activation), edema (in both injured and uninjured tissue), abdominal visceral swelling leading to abdominal hypertension and the abdominal compartment syndrome, and ultimately multiple organ failure (104,105).

Hemoglobin-based Oxygen Carriers

In the last decade several hemoglobin based oxygen carriers (HBOCs) have moved to clinical trials. These hemoglobin solutions are either human or bovine in origin and consist of hemoglobin dimers or tetramers. The half-life of the HBOCs is approximately 20 to 23 hours (106,107). Early results have been promising, demonstrating that HBOCs are capable of replacing all or part of the transfusion requirement in trauma and surgery (108,109). Advantages of these solutions are that some require no refrigeration; no cross-matching is necessary, small vessel and microcirculation oxygen transport is enhanced, and therefore tissue oxygenation improves (110). In one animal study, low volume resuscitation from profound hemorrhagic shock to a mean arterial pressure of 60 mm Hg with HBOC-201 allowed all animals to survive with no detectable major organ injury (111). The solutions do not appear to interfere with pulse oximetry although hemoglobin assays are distorted based on the percentage of HBOC in the plasma (112).

One potential disadvantage is that HBOCs raise systolic blood pressure by vasoconstriction, possibly through nitric oxide (NO) scavenging. New generation HBOCs have been tested in animals with improved results for resuscitation (113). At this writing it is not clear if HBOCs can be used completely in lieu of blood transfusion and whether the elevation in blood pressure poses a clinical problem for trauma patients. The HBOCs are capable of interfering with some other laboratory tests including: bilirubin-direct, creatine kinase MB-fraction (CK-MB), creatine kinase (CK), gamma-glutamyltransferase (GGT), magnesium, and uric acid (114). If HBOCs are to be routinely used, alternate testing methods will need to be developed. New technology is becoming available which allows clinicians to detect the levels of administered hemoglobin (115). A polymerized bovine hemoglobin (Hemopure^{TM}) has been approved for clinical use in South Africa. It will be interesting to evaluate its effectiveness in widespread clinical use.

Recombinant Erythropoietin

Erythrocyte production may be suppressed after hemorrhagic shock due to the effects of a variety of cytokine mediators of the systemic inflammatory response (116). Even with elevated levels of erythropoietin (EPO), erythrocyte production may be inadequate. Supranormal levels of EPO achieved by administering recombinant EPO have established a robust erythrocytic response in this seriously injured patient population (117). EPO receptors reside in diverse tissues and several studies document that EPO is capable of preventing neuronal apoptosis and cell death (118). Animal studies demonstrate that EPO is capable of improving survival from shock (119,120). Recent work in our laboratory (and confirmed by others), shows a rapid ameliorating effect on acute blood loss by erythropoietin (EPO) (121). The effect is significant ($p < .001$) within 48 hours, but is readily detectable earlier. In our study, rabbits subjected to a calculated 30% circulating blood volume loss showed 33% higher hemoglobin counts at 48 hours compared to control groups receiving no treatment. (Fig. 22.3) The early provision of EPO to trauma and burn patients may significantly reduce transfusion requirements and exert other beneficial hemodynamic and organ protective effects as well.

A double blind study by Corwin et al. (122) showed that 300 units per Kg of recombinant erythropoietin administered on a predetermined regimen to anemic ICU patients reduced transfusion requirements by half. Interestingly, the benefits of EPO were identified on the second or third day after administration, too early to expect significant erythrocytosis to have been a role.

Therapy with Coagulation Factors

Trauma patients receiving multiple transfusions develop coagulopathy in part from hemodilution as well as consumption of coagulation factors. More than 70% of trauma

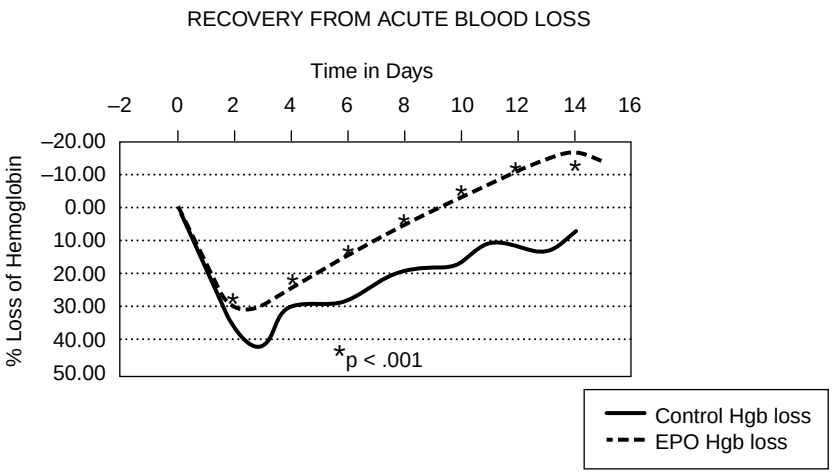

Figure 22.3 Effect of erythropoietin (EPO) on 30% blood loss in rabbits.

patients receiving more than 10 units of packed red cells develop clinical and laboratory evidence of coagulopathy (123). Measurement of coagulation parameters, platelets, and individual factors (or factor inhibitors) is essential to guide component therapy for the multiply transfused patient. Hypothermia and acidosis in the trauma patient are associated with increased mortality. (124) They adversely affect coagulation and require correction for resuscitation to be optimal. Prothrombin and partial thromboplastin times are elevated in the acidotic and hypothermic patient and have been associated with increased use of blood products and poorer outcome (125). By warming the patient, the administrated resuscitation fluids and blood products, and attention to correction of acidosis through appropriate resuscitation, the coagulopathy associated with hypothermia and acidosis can be avoided and outcome improved.

Factor VIIa

Recombinant factor VIIa (rFVIIa) is a 406 amino acid, vitamin K-dependent glycoprotein analogous to hepatically synthesized factor VIIa. Factor VIIa is activated by tissue factor and assists in the production of a fibrin clot (126). Recombinant factor VIIa is indicated for treatment of bleeding in a selected group of hemophilia patients but has been increasingly used in unapproved indications such as the treatment of bleeding in trauma and nontrauma patients (127). A review of the published literature by our staff revealed 29 reports of the use of rFVIIa in surgery in 326 patients. The majority of these reports were anecdotal. Typically rFVIIa was used for the control of hemorrhage when all other measures had failed. In these coagulopathic individuals rFVIIa showed great promise, frequently stopping bleeding, reducing blood requirements dramatically, and improving clotting parameters. In a randomized retropubic prostatectomy trial, where rFVIIa was given at the beginning of operation to noncoagulopathic subjects, blood loss was reduced by more than one half; patients receiving rFVIIa required no packed red blood cells while untreated patients required transfusion using an algorithmically driven transfusion protocol (128). A randomized study of the effects of rFVIIa administered preoperatively to non-coagulopathic partial hepatectomy patients showed a 30% blood loss reduction when administered at 80 micrograms per Kg (129). While the response to rFVIIa appears to be dose related, no evidence-based dosing regimens for noncoagulopathic trauma or surgical patients exist. Still, rFVIIa has the potential for hemorrhage control and reduction of blood loss for trauma patients. Data from a recently completed trial in Europe may answer this question. Nonetheless, certain conclusions may be drawn from the available literature: (a) VIIa is effective in reducing bleeding in coagulopathic humans (liver disease, dilutional coagulopathy, hemophilia), (b) further studies are required before rfVIIa can be recommended for noncoagulopathic surgical or trauma patients, and (c) There appears to be a dose response in trauma patients and we do not yet know optimum dose of rfVIIa for trauma patients.

Desmopressin Acetate

Desmopressin acetate (DDAVP) is a synthetic analog of vasopressin. It initiates the release of von Willebrand factor (vWF) and increases vWF and Factor VIII (FVIII) in normal subjects by threefold to fivefold (130). It is administered intravenously in a dose of 0.3 micrograms per kg with peak plasma levels occurring 30 to 60 minutes after administration. The plasma half-life is 5 to 8 hours for FVIII and 8 to 10 hours for vWF (131). DDAVP has been well utilized as a platelet function adjunct in patients with uremia from renal failure.

Fresh Frozen Plasma

Fresh frozen plasma (FFP) has been frozen within 6 hours of collection and is utilized for its clotting factor content in trauma resuscitation. No specific rule has been agreed upon for the FFP to the bleeding trauma patient. Ideally one would identify specific coagulopathies before administering FFP. However, in the presence of massive bleeding (requiring more than one blood volume replacement of red cells) or coagulopathy, many practitioners empirically administer one unit of FFP for every four or five units of red cells administered (132). Clotting times, fibrinogen levels, and platelets should still be checked, even if FFP must be administered before the results are known. Rapid administration of FFP in children, particularly through a central line, has been associated with cardiac arrest (133). A transient decrease in ionized calcium is thought to be causative. In children FFP should be administered slowly and peripherally if possible. If whole blood is available for resuscitation FFP is usually unnecessary.

Cryoprecipitate

Cryoprecipitate is obtained by slowly thawing frozen plasma and contains high concentrations of Factor VIII, von Willebrand Factor, and fibrinogen (134). If FFP is used to supplement massive transfusion, cryoprecipitate is likely unnecessary unless fibrinogen levels fall. If the fibrinogen level falls to below 100 mg per dL cryoprecipitate may be necessary (135). Cryoprecipitate comes in 5 to 20 mL units containing 80 to 120 units of Factor VIII. It is usually administered ten units at a time to an adult and titrated according to Factor VIII and fibrinogen deficiencies (136).

ASSESSING THE RESULT

Tissue Oxygen Consumption (VO_2)

Maintenance of tissue oxygen consumption (VO_2) is essential for survival from massive hemorrhage. VO_2 is increased following blood loss by an increase in heart rate and systemic oxygen extraction if volume replacement is not immediately available (myocardial oxygen extraction is constant) (137). For severe hemorrhagic shock casualties who have maximized O_2 extraction, O_2 consumption becomes delivery dependent (Fig. 22.4). Optimal resuscitation probably requires supramaximal O_2 delivery in these patients (138–140). Attempting to increase O_2 delivery by increasing only O_2 saturation with supplemental normobaric O_2 lacks potency and is insufficient. Crystalloid fluid resuscitation increases stroke volume, cardiac output, and oxygen delivery. However, considerable deficits in microcirculatory end organ perfusion and tissue oxygenation persist after crystalloid and/or stored packed red blood cell infusion leading to common complications including multiorgan failure (MOF) (141). Thus, maximizing O_2 delivery to support VO_2 by replenishment of O_2 content with hemoglobin or an alternative oxygen carrier may be needed to improve survival beyond existing rates (142). Preclinical studies have highlighted the efficacy of low volume hypotensive resuscitation using bovine polymerized hemoglobin, an oxygen therapeutic or carrier (143–145). However, as a general rule, VO_2 must be maximized to benefit from blood transfusion for hemorrhage.

Cardiac Output

Cardiac output is a useful monitor of the adequacy of resuscitation following hemorrhage. Decreased central vital signs, such as blood pressure, and cardiac output correlate well with poor outcomes, while normal values do not predict good outcomes (146). For example, a systolic blood pressure < 90 on arrival into the trauma bay correlates well with the relative risk of death, especially in the elderly. Thus, in addition to blood pressure, cardiac output, oxygen delivery, tissue pO_2, and indirect indicators of adequacy of resuscitation such as base deficit (on arrival) and arterial lactate provide utility in guiding and assessing the adequacy of resuscitation. A variety of other surrogate cardiac output monitors such as sublingual capnometry, and lithium dilution techniques may have utility as well, but remain to find their place in the current armamentarium.

Tissue Perfusion

An indirect measure of tissue perfusion may be obtained through the interrogation of base deficit. Because of the switch from aerobic to anaerobic metabolism in severe shock, metabolic acidosis develops. The degree of metabolic acidosis closely correlates with survival from hemorrhagic shock (147). Any degree of metabolic acidosis in the hemorrhaging patient should be quickly corrected through restoring adequate tissue perfusion and oxygenation. Other measures of inadequate tissue perfusion are low arterial pO_2, high respiratory rate, low glucose and low oxygen saturation, cool extremities, and disordered mentation. Base deficit correlates with the adequacy of resuscitation in burn patients and has been demonstrated to enjoy greater utility than pH or volume of resuscitation fluids in predicting outcome. Base deficit is not perfect as a risk or resuscitation marker. Base deficit's fidelity as a marker of the risk of death is in part age and mechanism of injury dependent. As demonstrated by Rutherford, et al., (148) the LD50 for patients under the age of 55 versus over the

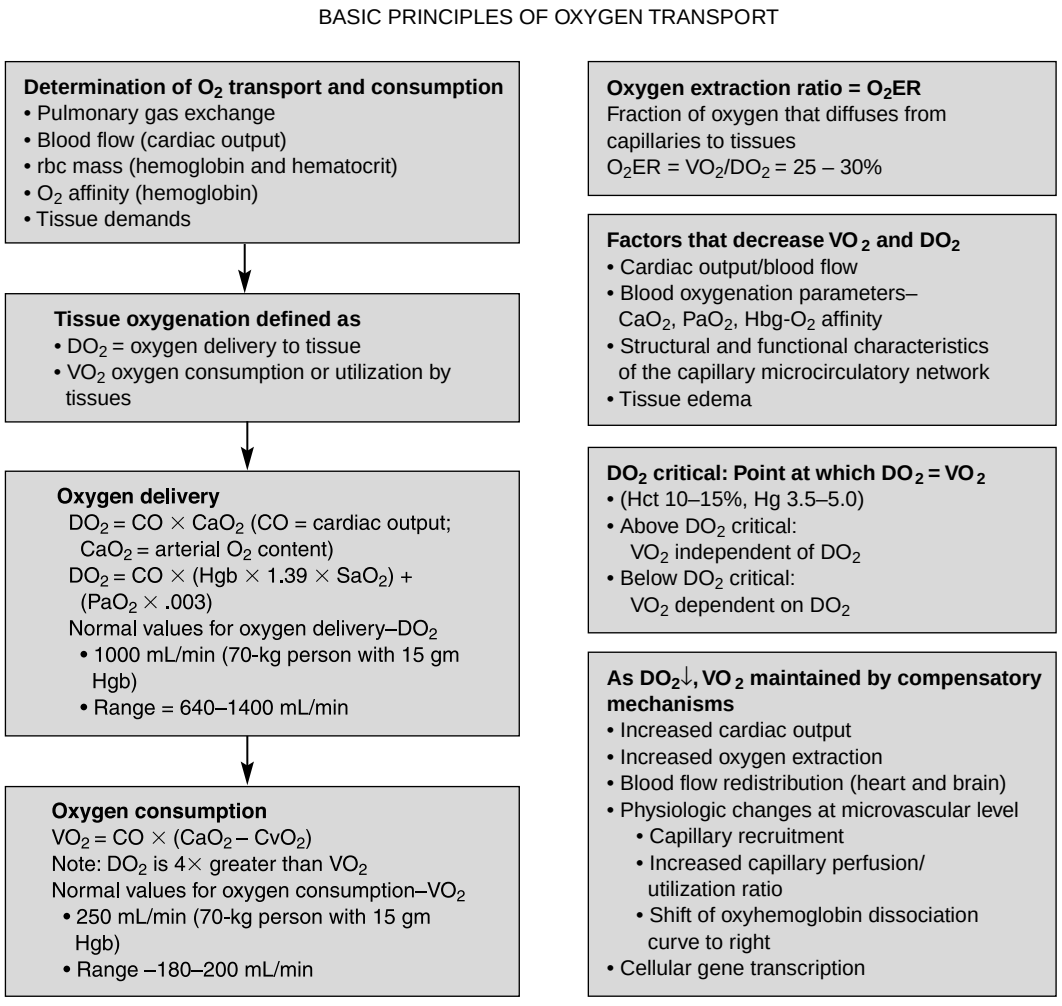

Figure 22.4 Basic principles of oxygen transport.

age of 55 was different. However, the addition of a traumatic brain injury to the under 55 age group shifted their LD 50 curve so that it matched that for the older patients. More recent studies have identified different values for lethality for patients with other injury complexes as well (149–152). Moreover, the base deficit will reflect nonmetabolically generated acid as well. Resuscitation-induced hyperchloremic acidosis will be identified as a low base deficit, even in a well resuscitated patient, making utility after resuscitation problematic (153). Instead, arterial lactate may represent a marker with less situational specific utility.

Lactate

Arterial lactate closely correlates not only with survival, but also the relative risk of infectious complications after resuscitation (154,155). Lactate represents the majority of metabolically generated acid that is detected by the base deficit and represents the anaerobic end product of glucose consumption for ATP generation. Lactate is useful not only as an isolated value, but as a trended value. Resuscitation adequacy is linked to resolution of lactic acidosis. Well resuscitated patients (normal heart rate, adequate cardiac output, reduced volume requirement, and so on) who still evidence an elevated arterial lactate may have one of three conditions: (a) inadequate resuscitation (occult hypoperfusion), (b) hyperlactatemia (normal pH, normal lactate/pyruvate ratio), or (c) subclinical seizures (elevated lactate from muscle and neuronal activity). Clearly, the first requires additional plasma volume expansion and red cell transfusion if there is significant anemia. The second requires benign neglect, while the third requires investigation in the appropriate clinical setting.

Tissue PO_2

Ideally, one would like to measure tissue pO_2 in all injured tissues as well as critical organs such as heart, brain, lung,

liver, and kidney. With current technology, this is not feasible outside the laboratory. However, measurement of transcutaneous pO_2 is possible and is a reliable indicator of the adequacy of tissue oxygenation of the patient as well as in the injured extremity (77). A low tissue pO_2 (< 50 mm Hg) in uninjured tissue, and below 30 mm Hg (on room air) for injured tissue, correlates with death of the individual or injured part (74,156). Transcutaneous oximetry ($TcpO_2$) machines are noninvasive, easy to use, and provide reliable information on oxygenation status. They have been clinically implemented on neonates and in patients with peripheral vascular disease. Invasive and indirect infrared muscle oximetry has also been used experimentally to assess the adequacy of resuscitation from hemorrhagic shock with some encouraging results (157,158). $TcpO_2$ is a reliable method for identification of early resuscitation problems and provides objective criteria for setting physiologic goals and adjusting therapy (159). As the hemoglobin based oxygen carriers come into use, $TcpO_2$ may be the preferred method of assessing adequacy of resuscitation if traditional pulse oximetry proves unreliable in this setting (160).

CONCLUSION

The transfusion of blood products in trauma and burn patients can be lifesaving. Blood transfusion also carries

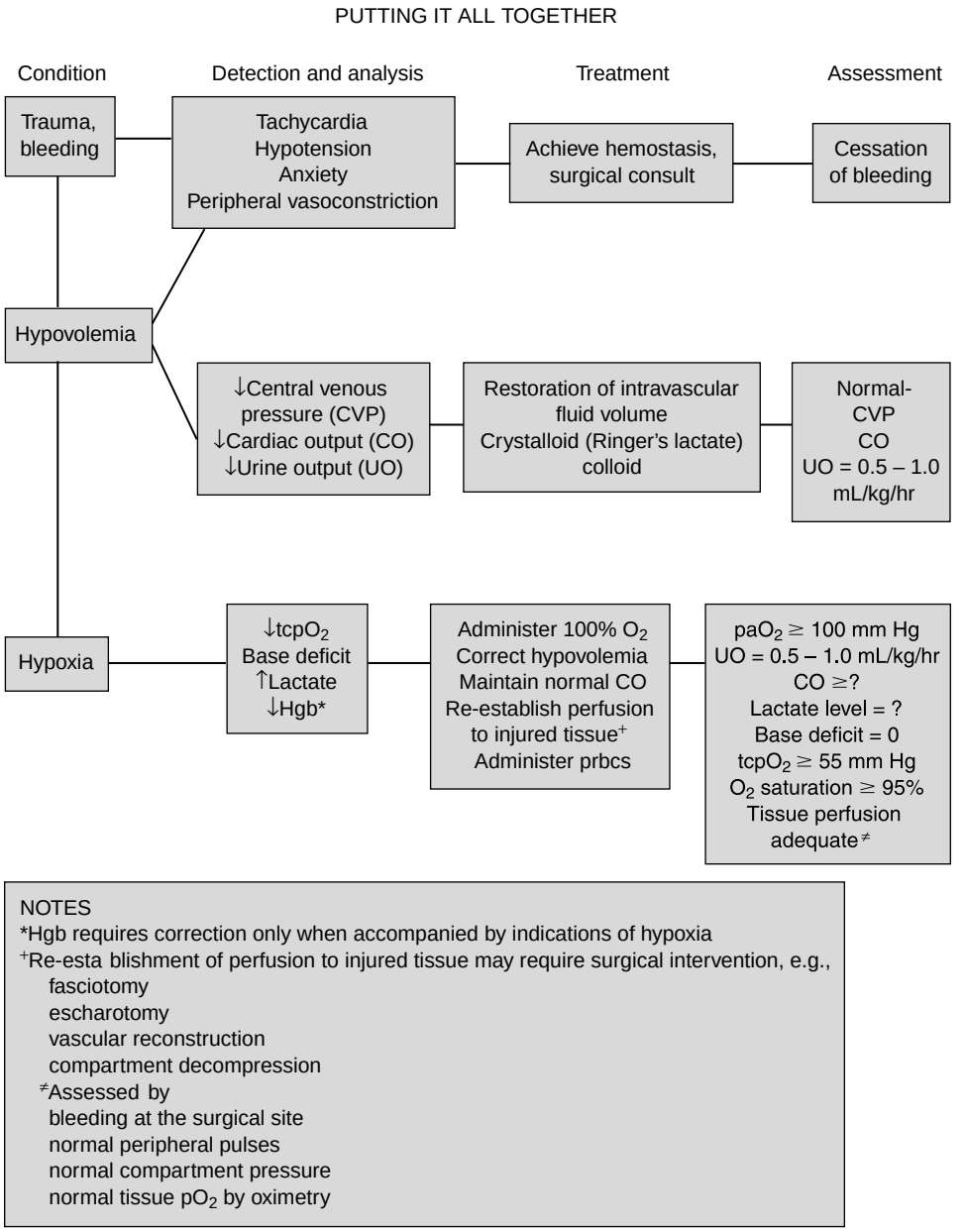

Figure 22.5 Putting it all together.

the risk of transfusion reaction, infection, immunosuppression, and posttraumatic and surgical complications. Prior to administration of blood products, treatment algorithms should be consulted and followed so that blood product use is minimized, blood products are used efficaciously, and treatment outcomes are maximized. (Fig. 22.5) Conditions which affect tissue oxygenation such as active hemorrhage, hypovolemia, poor cardiac and pulmonary function, acidosis, and poor tissue perfusion should be corrected prior to blood transfusion, or in the case of extreme emergency, concurrently with blood transfusion. The efficacy of blood transfusion should be determined by outcome measures linked to physiologic performance and tissue oxygenation, rather than through hemoglobin levels alone.

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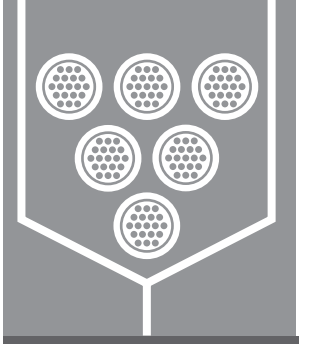

23

Acute Gastrointestinal Bleeding and Transfusion Management

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Although the majority of patients treated for gastrointestinal hemorrhage are transfused, treatment recommendations rarely include clear guidelines on blood management. In this chapter, we review the diagnosis and treatment of gastrointestinal hemorrhage as well as the impact of current standards on allogeneic blood transfusion. Risks associated with allogeneic blood transfusion are presented elsewhere in this text, as are reasons for transfusion avoidance. Consequently, our approach assumes that the reader understands and agrees with the above and focuses on a treatment strategy of gastrointestinal hemorrhage that limits allogeneic blood use.

SCOPE OF THE PROBLEM

Acute gastrointestinal hemorrhage poses a significant medical problem in the United States. Approximately 1% to 2% of all hospital admissions annually are attributed to this entity (1). Data from 1992 to 1999 from the National Hospital Discharge Survey found an annual hospitalization rate for upper gastrointestinal bleeding ranging from 149 to 172/100,000 (2). A recent U.S. population-based study estimated an annual incidence rate of lower gastrointestinal bleeding at 20.5/100,000 (3). In our institution we had 21,601 admissions for fiscal year 2004. Of these, 325 were admissions for gastrointestinal bleeding (1.5%; DRG 174) and of these 210 were transfused with packed red blood cells (65%). In addition, morbidity and mortality of this entity has remained relatively stable over the last 45 years with an incidence of approximately 10% despite transfusion (4–7).

Historically, transfusion of red blood cells to treat acute hemorrhage was recommended primarily to restore volume losses (8). As blood became more available and as measurement of hemoglobin and hematocrit levels increased in popularity, the reason for transfusion gradually shifted from a clinical basis to a numeric one. In 1942, Adams and Lundy (9) reported and recommended maintaining a hemoglobin level of 10 g per dL based on their clinical experience. In subsequent years, this so called 10/30 rule ignored a patient's clinical status and led to many unnecessary transfusions. The rule persisted until the early 1980s when attention was shifted to clinical assessment and a lowered transfusion trigger.

TRANSFUSION AND GI BLEEDING

Transfusion has been used for years to support patients with gastrointestinal bleeding. This may be based in part on the observation that bleeding often will stop without any intervention, and in part, on the lack of currently available diagnostic tools. In 1984, Morris et al. (10) advocated such watchful waiting, stating: "the patient might be

accorded the luxury of two rebleeding episodes rather than one or a maximal blood replacement within 24 hours of six units rather than four before any intervention". Until recently it was common practice to refer patients for surgery only after a given transfusion limit had been reached. Some sources promoted transfusion of eight units of blood in a young patient and five units in an older patient before any surgical attempt was made to stop the bleeding (11). Transfusion rationale in acute gastrointestinal bleeding patients came from the worlds of both clinical observation (i.e., transfuse after four to six units of blood had been lost) and numbers (i.e.,transfuse when hematocrit falls below 30%). Transfusion was considered standard of care and was often used to sustain patients while a diagnosis was made and/or while waiting for therapy to have an effect. Few, if any, reports of treatment of patients with gastrointestinal bleeding identified a transfusion risk (12,13).

It was noted as early as the 1930s that transfusion of blood for hemorrhage might not improve prognosis but also was associated with an increase in patient mortality (14). More recent evidence points to the potential hazard and lack of benefit of transfusions in the setting of acute hemorrhage (15). First, young clot formed in, and around a, vessel is fragile and can be dislodged if the compensatory hypotension and vasoconstriction are abolished by aggressive repletion of blood volume. Second, a case-control comparison of patients that were transfused for hemorrhage against those who were not showed a highly significant increase in clotting time in the former patients, which created a potential risk for further bleeding (16). Third, there is compelling evidence that stored blood presents numerous and varied risks to the patient, as described elsewhere in this text (17). Existing treatment algorithms for gastrointestinal hemorrhage speak to the need for using transfusion primarily as volume replacement in resuscitation, but have not defined its value, especially in light of current guidelines that recommend use of blood to improve tissue oxygenation. Asanguineous resuscitation fluids including saline, lactated Ringer's solutions, and colloids such as hydroxyethyl starch are perfectly capable of increasing oxygen delivery by replacing lost blood volume (18,19). Moreover, allogeneic, stored blood is an inefficient oxygen carrier because significantly loss of 2,3 disphosphoglycerate increases red blood cell affinity for oxygen, thus impairing its release. Dawson (20) and others (21) demonstrated that transfusing three units of 7-day-old blood decreased the oxygen supplies for up to 24 hours.

The evidence for and against transfusion in gastrointestinal hemorrhage is limited. Existing reports favor a decision to transfuse using clinical scoring systems derived from history, physical signs, and admission laboratory values (22–24). Most of these studies were designed to evaluate the benefit of an intervention such as endoscopy, so their relevance to the transfusion decision is debatable. The value of transfusion and watch and wait practices in gastrointestinal bleeding patients has been brought into question by several studies of restrictive versus a liberal hemoglobin threshold for transfusion that have shown no benefit from more blood in improving patient morbidity and mortality for up to 120 days after transfusion. The Transfusion Requirements in Critical Care Investigators Group (TRICC) study prospectively randomized 838 critically ill ICU patients with hemoglobin under 9 g per dL to one of two transfusion strategies (25). A control group of liberal transfusion practices allowed transfusion of blood to maintain hemoglobin above 10 g per dL. In the restrictive group patients only received transfusions of blood product when their hemoglobin fell below 7 g per dL. The results showed that the in-hospital mortality rate was significantly lower in the restrictive group. One must conclude that transfusion of four to eight units of blood in anticipation of bleeding cessation may produce more harm than good.

IDENTIFICATION AND TREATMENT OF GASTROINTESTINAL BLEEDING

Treatment of gastrointestinal bleeding depends on its cause and location. Causes of gastrointestinal hemorrhage can be categorized as either upper or lower in origin. By far, the majority of cases of GI hemorrhage are caused by upper GI bleeding. Upper GI bleeding accounted for 76% of bleeding events reported in the 1997 American College of Gastroenterology Bleeding Registry (26). Duodenal and gastric ulcers were the source in more than 50% of the upper GI bleeders. Diverticulosis was the most common bleeding source found in lower GI bleeders; 78.8% of patients were anemic, with 60.9% having a hemoglobin level of $<$10 g per dl. 31% had either orthostatic changes in blood pressure or shock; 58.2% received blood transfusions. Rebleeding (11.2%), need for surgery (7.1%), and fatalities (2.1%) were uncommon.

Some authors also separate and distinguish upper GI bleeding as variceal or nonvariceal, given that the definitive treatment is different. The causes of bleeding are listed in Tables 23.1 and 23.2. As with any critical patient the initial triage includes assessment of the airway, breathing, and circulation. Two large bore peripheral intravenous lines for access, a urinary catheter, and preliminary blood work should be done immediately. Once this has been accomplished, the determination of the severity of bleeding needs to be addressed. We believe *severity* includes both the amount of blood already lost and the

TABLE 23.1
CAUSES OF UPPER GI HEMORRHAGE

Lesions proximal to ligament of trietz
Peptic ulcer disease
Duodenal ulcer
Gastric ulcer
Gastroesophageal varices
Mallory-Weiss tear
Stress gastritis
Dieulafoy's lesions
Esophageal, gastric or duodenal tumors
Aortoesophageal or aortoduodenal fistula
Esophagitis
Angiodysplasia
Hemobilia
Pancreatitis induced psuedoanuerysm
Coagulopathy
Iatrogenic injury
Ischemia
Severe epistaxis

rate of current bleeding. Acute assessment is often difficult because blood is mixed with GI fluids; nonetheless assessment of degree of blood loss is critical in choosing the means to resuscitate a patient. Current guidelines from the trauma literature are presented in Table 23.3 (27). Note that crystalloid is the recommended replacement fluid for volume losses up to 2,000 ml. We also recommend the use of colloid solutions, such as balanced hetastarch, to restore blood volume particularly after active bleeding has been controlled. Note also that these guidelines do not address red blood cell transfusion as an oxygen carrier. This may reflect the fact that oxygen delivery is a function of circulating volume more than absolute red blood cell mass.

TABLE 23.2
CAUSES OF LOWER GI HEMORRHAGE

Lesions distal to ligament of trietz
Colonic diverticular disease
Colonic vascular ectasia
Small intestinal diverticular disease
Meckel's diverticula
Psuedodiverticula
Inflammatory bowel disease
Chronic ulcerative colitis
Crohn's disease
Neoplasms
Colonic
Small intestine
Aortoenteric fistula
Colitis
Infectious
Ischemic
Radiation-induced
Angiodysplasia
Trauma
Iatrogenic injury
Coagulopathy
Hemorrhoids

Diagnostic approaches to assess bleeding vary according to anatomy. Several modalities provide information with regard to location; some are more specific than others (Table 23.4). History and physical are always the mainstays for gathering information and can provide clues as to the etiology of the source of the bleeding. For example, a history of NSAID consumption or previous epigastric pain may point to a peptic ulcer or gastritis. Weight loss and early satiety may lead the clinician to consider a neoplastic origin. These are but two examples of a large list that may point the astute clinician in the right direction. Nasogastric tube placement with return of either blood (bright red or coffee grounds) or clear bile helps to identify the source as upper or lower in origin.

Radionucleotide scanning is often used to assess bleeding sources in stable patients who are thought to be bleeding at a rate too slow to be seen on arteriogram. This diagnostic approach is generally more sensitive (0.5 ml per min of blood to detect bleeding) than arteriography (1 ml per min of blood to detect bleeding). However, it is limited in that it can only define right versus left and may be unable to differentiate upper from lower gastrointestinal sources. These initial studies can help localize the source of bleeding, which in turn will help to identify a more definitive strategy for therapy.

Endoscopy

Endoscopy is both a diagnostic as well as a potential therapeutic modality for gastrointestinal bleeding. Over the last several years urgent endoscopy to stop GI bleeding has had success rates in the 75% to 90% range (28,29). Wilcox and Clark (30) demonstrated that early intervention with endoscopy minimized the need for operative intervention and lowered the mortality rate for both upper and lower GI bleeding. Ohta et al. (31) successfully stopped initial bleeding in 44 patients who presented in severe shock using endoscopic hemoclip application. Survival was less in those patients with more severe shock, suggesting that time to treatment played a role. Oxner et al. (32) randomized 93 patients with peptic ulcer bleeding and a visualized bleeding vessel to either endoscopic injection of epinephrine or standard treatment. The treated group had lower mortality (4 [8.3%] versus 9 [20%]), less rebleeding (injected 8 [16.7%] versus control 21 [46.7%], $p = 0.011$), less need for surgery (4 [8.3%] versus 8 [17.8%]), and fewer blood transfusions (5 versus 7.5 units).

TABLE 23.3
FLUID RESUSCITATION GUIDELINES

	Mild	Moderate	Severe	Massive
Blood Loss (mL)	<750	750–1500	1500–2000	2000
Pulse rate	>100	>100	>100	>100
Blood pressure	Normal	Normal	Decreased	Decreased
Urine output (ml/h)	>30	20–30	5–15	Negligible
Mental status	Anxious	Confused	Lethargic	Delirious
Volume replacement	Crystalloid	Crystalloid	Crystalloid	Blood

(Adapted from Thomas B. *Trauma.* In: Lee KF, Dyke CM eds. Surgical Attending Rounds. Philadelphia, Pa: Lee & Febiger; 1992.)

Adjunctive, medical therapy can also improve outcomes and reduce transfusion need. The European Acute Bleeding Oesophageal Variceal Episodes (ABOVE) randomised trial showed that early administration of somatostatin in conjunction with sclerotherapy was more effective than placebo in the overall control of acute variceal haemorrhage in patients with cirrhosis (33). The mean transfusion volume during the trial period (120 hours) was 2.64 (SD 0.35) units in the somatostatin group versus 3.62 (0.35) units in the placebo group ($p = 0.05$). Which patients should undergo urgent endoscopy? Kalula et al. (34) examined the correlation between multiple variables and outcome in 200 consecutive patients with hematemesis or melena. Eighty patients (40%) had a good outcome, defined as no blood transfusion, endotherapy, or surgery, and alive at 1 month following presentation. These patients had a presenting hemoglobin level of >10 g per dl, no melena and no syncope, suggesting that urgent endoscopy could be avoided under these circumstances. Adamopoulos et al. (28) identified predictors for the likelihood of active, upper GI bleeding that can be used to identify those patients who would benefit most from upper endoscopy. A multivariate analysis of 17 variables identified four criteria that were associated with active bleeding. (Table 23.5) The authors created relative point values by stratifying each criterion using an adjusted odds ratio. They were able to extrapolate this into a classification tool with the following formula:

Number of points
= 6(Red Blood on NGT) + 4(Hemodynamic instability)
+ 4 (hemoglobin <8 g/dL) + 3 (WBC >12,000)

The overall point total can range from 0–17. Table 23.6 indicates the likelihood that active bleeding would be present based on point total. These criteria promote evaluation by upper endoscopy within the first 12 hours of admission/consultation to improve patient outcome. One study by Bourienne et al. (35) indicated that the only significant predictor of rebleeding was hypovolemia on admission. Blatchford et al. (24) use a similar but more complex risk score from patients' admission hemoglobin, blood urea, pulse, and systolic blood pressure, as well as presentation with syncope or melena, and evidence of hepatic disease or cardiac failure. Regardless of the scoring system used, the

TABLE 23.4
MODALITIES FOR ASSESSING GASTROINTESTINAL HEMORRHAGE

Diagnostic (relative)
History and physical
Rectal exam / Evaluation of stool (melena vs. bright red)
Nasogastric tube insertion
Radionucleotide scanning
Contrast studies (barium)

Diagnostic and therapeutic
Endoscopy
Colonoscopy
Arteriogram
Surgery

TABLE 23.5
CRITERIA AND POINT VALUES FOR ACTIVE UGI BLEEDING

Criteria	Relative Point Value
Red Blood on nasogastric aspiration	6
Presence of hemodynamic instability	4
Hemoglobin <8 g/dL	4
White blood cell count >12,000	3

(Adapted from Adamopoulos A, Baibas NM, Efstathiou SP, et al. Differentiation between patients with acute upper gastrointestinal bleeding who need early urgent upper gastrointestinal endoscopy and those who do not. A prospective study. *Eur J Gastroenterol Hepatol.* 2003;15:381–387.)

TABLE 23.6
LIKELIHOOD OF ACTIVE UGI BLEEDING

Number of Points	Percent with Active Bleeding (Internal Study)	Percent with Active Bleeding (External Study)
0–3	0	0
4–6	5	2.6
7–10	58	10
11–17	89	96.3

(Adapted from Adamopoulos A, Baibas NM, Efstathiou SP, et al. Differentiation between patients with acute upper gastrointestinal bleeding who need early urgent upper gastrointestinal endoscopy and those who do not. A prospective study. *Eur J Gastroenterol Hepatol.* 2003;15:381–387.)

key factor in improving outcomes and decreasing overall transfusions in patients with gastrointestinal bleeding is rapid identification of those who are actively bleeding. We illustrate this approach with one of our patients.

An 81-year-old African American male, presented to our emergency department (ED) with a recent history of passing a mahogany colored stool from his colostomy. According to the patient's niece, he had had hematemesis in the early morning hours prior to admission. The patient denied any pain. There was no evidence of use of ASA or NSAIDS. Blood work drawn in the triage area indicated an initial WBC count of 7.4 K per L, hemoglobin of 12.1 g per dL, and hematocrit of 36.9. After evaluating the patient the ED physician had 2 large bore IVs placed. A nasogastric tube was placed after the patient had another episode of hematemesis. On initial aspiration the NGT drainage was approximately one liter of bright red blood. The patient became hypotensive (73/50) and tachycardic (125 bpm). Repeat hemoglobin and hematocrit were 8 g per dL and 25.6 % respectively. WBC count was still within normal limits at 6.6 K per L. The patient scored 14/17 (6+4+4) based on the classification tool created by Adamopolous et al. (28). Surgery, critical care, and gastroenterology had evaluated the patient within 40 minutes of consultation. The plan was to do upper endoscopy once the patient was more stable. After asanguineous fluid resuscitation, the patient's blood pressure was 100/60 and endoscopy was performed. Active bleeding was noted at the esophagogastric junction from an area of ulceration. Hemoclips were applied to the area and the bleeding ceased. The patient's blood pressure quickly improved to 124/75. The patient remained tachycardic and he was ultimately transfused one unit of leukocyte reduced packed red blood cells. The rapid assessment and early intervention limited this patient's exposure to the risk of transfusion.

Evidence supports the use of endoscopy for both upper and lower GI bleeding. In the past, many thought endoscopy inadequate for visualization of the colon because of blood obscured the mucosa. However, recent literature indicates that after an oral bowel preparation the diagnostic yield of colonoscopy is as high as 90% (36). Other authors contend that even without any mechanical preparation the yield is as high as 76%, since the blood acts as a cathartic cleansing agent (37). In either case, early evaluation and intervention play vital roles in improving patient outcome. Garcia Sanchez et al. (38) evaluated urgent versus elective colonoscopy in a series of 50 patients who presented with lower GI bleeding. Accurate endoscopic diagnosis was more frequently established with early colonoscopy than with elective colonoscopy (15 [47%] versus 2 [15%], $p < 0.05$).

ANGIOGRAPHY AND ANGIOTHERAPY

Small vessel angiography has rapidly changed how gastrointestinal hemorrhage is both evaluated and treated. Angiography has a sensitivity threshold of approximately 1 ml per minute for active bleeding, but bleeding rates as low as 0.4 ml per min have been detected (39). Eisen et al. (40) recently reported an overall success rate of 40% to 78% for the Standards and Practice Committee of Gastrointestinal Endoscopy. Ryan and colleagues have pushed the envelope in patients with suspected but unproven bleeding with their successful use of intra-arterial, provocative mesenteric angiography with heparin, vasodilator, and tPA in a small series of patients with occult gastrointestinal bleeding. This technique identified the site of bleeding in 37.5% of patients and contributed to treatment in 50%.

Historically, bleeding below the above threshold was considered nondiagnostic and was not treated with intra-arterial infusion of vasoconstrictors or embolization. However, recent reports show that once a bleeding site is identified on arteriography, treatment can be highly successful (42).

Intravenous infusions of vasoconstrictors have a long history of success in treating upper GI hemorrhage. A randomized trial of high dose versus low dose terlipressin in patients with bleeding varices showed that transfusion requirements were lower in the high dose group (43). The meta-analysis of 1,609 patients from 20 trials comparing terlipressin infusion to standard therapy by Iannuou et al. (44) showed that, compared to placebo, terlipressin reduced mortality (relative risk 0.66, 95% CI 0.49 to 0.88),

failure of haemostasis (relative risk 0.63, 95% CI 0.45 to 0.89) and the number of emergency procedures per patient required for uncontrolled bleeding or rebleeding (relative risk 0.72, 95% CI 0.55 to 0.93). When used as an adjuvant to endoscopic sclerotherapy, terlipressin reduced failure of hemostasis (relative risk 0.75, 95% CI 0.58 to 0.96), and had an effect on reducing mortality that approached statistical significance (relative risk 0.74, 95% CI 0.53 to 1.04). Intra-arterial infusion of vasoconstrictors, e.g., vasopressin or terlipressin, can control bleeding from diverticula and arteriovenous malformations (40,45). Vasoconstrictor therapy carries a complication rate of 10% to 20%, including arrhythmias, hypertension, and ischemia, both localized and cardiac (40).

Superselective embolization of gastrointestinal bleeding sites is rapidly replacing vasoconstrictor therapy, thanks primarily to the introduction of steerable, micro-catheters (46). Burgess and Evans (47) successfully stopped bleeding using this approach in 13 of 14 patients (93%). Waugh et al. (48) reports a 96% success rate over a 5-year period. Before the advent of superselective angiography, clinicians preferred not to use embolization to treat hemorrhage distal to the ligament of Treitz because of the area's limited collateral blood supply. However, in a retrospective review by Schenker et al. (49), aggressive, transcatheter embolotherapy of acute upper GI bleeding increased patient survival 13.3-fold compared to standard treatment. Transcatheter embolotherapy may lead to abdominal pain or intestinal infarction. Reports by Patel et al. (50) state that ischemic bowel injury rates of 15% to 35% from past studies using emobolization to treat lower gastrointestinal bleeding. However, he further states that since the introduction of superselective embolization, newer embolic agents and greater expertise of personnel performing procedures, the rate of injury has decreased. In fact, blind embolization (meaning embolization of a particular region without angiographic confirmation of bleeding) has been performed for upper gastrointestinal bleeding with satisfactory results (51). Embolotherapy is as successful as surgery for controlling endoscopy failures. Ripoll et al. (52) evaluated the usefulness of embolization versus surgery as salvage therapy for unsuccessful upper endoscopy. The embolotherapy patients were typically older and had a higher incidence of cardiac disease compared to the surgery group. There was no statistically significant difference in outcomes between embolization and surgery. The average transfusion requirements were also the same (approximately 4.1 units), which reflects a time delay secondary to the unsuccessful endoscopic therapy (52). Moreover, the majority of these studies indicate that the outcomes for lower GI bleeding when treated by embolization were equal to or better than surgery. Of particular note is that the patient populations treated with embolization in these series were generally older and had more cardiac comorbidities, suggesting that emoblization may offer successful control of bleeding without the risks of surgery.

Surgery

Surgery, while once the gold standard for treatment of gastrointestinal hemorrhage, now should be considered primarily in the setting of endoscopic and angiographic failure. This change reflects improvement in both technology and techniques (53). Chung (54) was able to report in 1997 that of 5,112 patients treated for peptic ulcer disease, only 3.5% required surgery. The mortality of this group was higher (12% versus 4.5%) than the overall group, but this difference probably reflects the facts that the operative group patients were sicker and had failed more conservative treatment. Hamoui et al. (11) identified several current indications for surgery in upper GI bleeding, most of which relate to endoscopy failure. (Table 23.7) These same indications can be applied to lower GI bleeding. Once a decision has been made to go to the operating room, there is no room for delay. Lessons learned from Jehovah's Witness patients with active GI bleeding prove that early surgery as opposed to a watch and wait approach stops bleeding and saves lives (55).

Transfusion should no longer be viewed as a necessary treatment for gastrointestinal bleeding or as a temporizing measure, nor should the amount of transfused blood be used as a mathematical determinant of the need for surgery. The risks of transfusion are too great to treat blood in such a cavalier fashion. A vast amount of evidence supports the understanding that gastrointestinal bleeding can be stopped successfully in the majority of patients with endoscopic and angiographic therapy. Moreover, evidence supports the fact that these approaches increase survival, decrease complication rates and limit the need for blood transfusion—all worthy goals. Common sense also tells us that early action to stop bleeding should decrease transfusion and its attendant risks.

CONCLUSION

The ultimate goal of any intervention in treating gastrointestinal bleeding is to keep the patient alive. A secondary goal is to avoid the need for excessive transfusion. Both can be accomplished by early interventions to stop the bleeding. Delay in the early recognition and early treatment of bleeding, regardless of its cause, while using transfusion as a safeguard is no longer an option.

TABLE 23.7
COMPARISON OF OUTCOMES BY SITE OF BLEEDING AND INTERVENTION

Site of Bleed	Author	Patients	Intervention	Outcome
Upper	Bourienne A, et al.	144	Endoscopy **Number undergoing endo:** 144/144 (100%)	**Therapeutic intervention:** 144/144 (100%) **Initial hemostasis:** 108/144 (75%) **Rebleed:** 39/144 (28%)
Upper	Wilcox C, Clark W	796	Endoscopy **Number undergoing endo:** 727/796 (91%)	**Therapeutic intervention:** 140/727 (19.6%) **Intial hemostasis:** 98/140 (70%) **Rebleed:** 42/140 (30%) **Final hemostasis:** 123/140 (87%) **Surgery:** 17/140 (13%)
Upper	Barkun A, et al.	1869	Endoscopy **Number undergoing endo:** 1421/1869 (76%)	**Therapeutic intervention:** 692/1869 (37%) **Rebleed:** 264/1869 (14.1%) **Surgery:** 121/1869 (6.5%)
Lower	Wilcox C, Clark W	165	Endoscopy **Number undergoing endo:** 150/165 (91%) Also having Upper Endo: 112/165 (68%)	**Therapeutic intervention:** 2/165 (1%) **Rebleed:** 33/165 (20%) **Surgery:** 16/165 (9.7%)
Upper	Aina R, et al.	75	Embolization **Identified at endo alone:** 29/75 (39%) **Identified at angio alone:** 24/75 (32%) **Identified at endo and angio:** 22/75 (29%)	**Therapeutic intervention:** 62/75 (82.5%) **Rebleed:** 5/75 (6%) **Surgery:** 0 (0%)
Upper	Ripoll C, et al	70	Embolization after Endoscopic failure Surgery after endoscopic failure **Embolization:** 31/70 (44.2%) **Surgery:** 39/70 (55.8%)	**Therapeutic intervention:** 70/70 (100%) **Rebleed:** Embol. 9/31 (29%); Surg. 9/39 (23.1%) **Repeat surg.:** Embol. 5/31 (16%); Surg. 12/39 (30%)
Lower	DeBarros J, et al	27	Embolization	**Therapeutic intervention:** 27/27 (100%) **Rebleed:** 6/27 (22.2%) **Surgery:** 5/6 rebleeders (83%); 5/27 total (19%) **Ischemia:** 2/27 (7.4%)–1 required surgery
Lower	Bandi R, et al	48	Embolization	**Therapeutic intervention:** 35/48 (73%) **Rebleed:** 12/48 (25%) **Surgery:** 8/48 (17%) **Ischemia:** 6/25 (24%)–all managed expectantly
Upper/Lower	Ledermann H, et al	10	Embolization **Identified at endo and angio:** 5/10 **Identified at angio alone:** 5/10	**Therapeutic intervention:** 10/10 (100%) Upper (3/10); Lower (7/10) **Complete hemostasis:** 8/10 (80%) **Surgery:** 2/10 (20%)
Upper	Hunt PS	201	Surgery (Emergent)	**Type of surgery:** V&P w/ undersew: 101/201 (50%); 10 Deaths (10%) Partial Gast. (B-II): 81/201 40%; 10 Deaths (12%) Antrectomy and Vagot: 16/201 (8%); 1 Death (6%)

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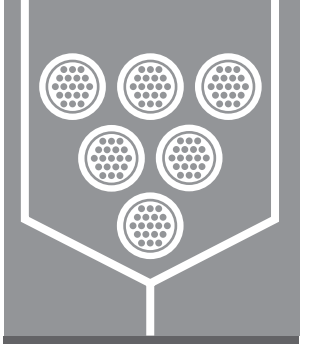

24

Coagulation in Trauma: Dilution and Massive Transfusion

Richard K. Spence ***Anthony Martinez***

Coagulopathy is a frequent finding in the trauma patient and may be caused by a combination of events including dilution of clotting factors and platelets following transfusion, hypothermia, and disseminated intravascular coagulation. Not surprisingly, trauma patients receiving massive transfusion are susceptible to developing coagulation abnormalities.

Massive transfusion is commonly defined as transfusion approximating or exceeding the patient's blood volume within a 24-hour period (1). However, in many trauma victims, this volume is administered within a shorter time interval. In this setting, blood losses of between 30% and 50% of total blood volume may be defined as massive hemorrhage. Although massive hemorrhage may result from gastrointestinal bleeding, ruptured aneurysms, and surgical procedures, (2,3) penetrating and blunt trauma are the leading causes of massive transfusion (4–8). Most series reviewing the outcome of massive transfusion are based on penetrating trauma. Penetrating injuries of the vessels of the neck, thoracic outlet, aorta, great veins of the chest and abdomen, or major intra-abdominal vascular injuries may require massive transfusion. Penetrating injuries of the liver may also be associated with intrahepatic vascular injury, or parenchymal injury alone may require massive transfusion. Proximal extremity injuries and near amputations as well may lead to such requirements. In blunt trauma, injuries of the pelvis, major abdominal and thoracic vessels, liver, spleen, and kidneys can lead to massive hemorrhage requiring massive transfusion.

Trauma patients are predominantly young males with an average age of 30 years (6–9). Overall survival among patients with massive transfusion is between 40% and 60% and correlates with number of blood transfusions. One series reported survival for massive transfusion in blunt trauma patients of 52% (8). In another series, survival rates ranged from 38% for patients with hepatic failure to 100% for obstetric cases (9). Vaslef et al. (10) identified 44 (0.6%) of 7,734 trauma patients admitted over a 5-year period who received >50 units of blood products in the first day. Overall mortality in these patients was 57%. Of the 25 deaths, 13 (52%) were caused by exsanguination.

Mobilization of emergency medical personnel, immediate resuscitation and transport, and improved surgical techniques have increased survival rates as high as 70% among patients requiring greater than 25 units of blood (7). Cinat et al. (11) credited more effective and efficient rewarming procedures, improved application of damage control techniques, more aggressive correction of coagulopathy, and improved blood banking procedures with improving survival from 16% to 45% in massively transfused patients treated over 10 years from 1988 to 1997.

Duration and magnitude of shock are critically important factors affecting mortality in massively transfused patients (12–16). Increasing age, severe head injury, abdominal trauma as a source of hemorrhage, pelvic fracture, underlying medical conditions particularly of hepatic origin, and nontraumatic surgical emergencies are associated with increased mortality in relation to blood loss and transfusion.

DILUTIONAL COAGULOPATHY

Clinical manifestations of dilutional coagulopathy include diffuse microvascular bleeding characterized by the onset of oozing from mucosa, raw wounds, and puncture sites. Although coagulopathy is predictable after increasingly larger volumes of blood and fluid replacement, an understanding of the principles of exchange transfusion helps clarify the concept of dilutional coagulopathy (4,17–19). The kinetics of exchange transfusion predict that nearly 37% of the original blood volume remains following the loss of a single blood volume (10 units in a 70 kg. adult) (13). Remaining levels of coagulation factors and platelets are usually adequate to maintain hemostasis. With two or three volume exchanges, these elements will drop to levels of approximately 15% and 5%, respectively. These levels serve only as basic estimates in the clinical setting, since both platelet counts and amounts of circulating clotting factors will vary depending on both rate of blood loss and rate of transfusion.

Platelet levels rarely fall below 100,000 until approximately one-and-a-half times the patient's blood volume has been replaced (4). Platelet counts above 100,000 usually provide adequate hemostasis unless a qualitative deficit is also present. The exact activity levels needed for hemostasis when multiple factor deficiencies coexist are not well defined. Dilution of coagulation factors during massive transfusion to a level of 30% functional activity may be associated with prolongation of prothrombin (PT) and activated partial thromboplastin (aPTT) times. With diminished factor activity, the prolongation of the PT and aPTT are reagent dependent and consequently are not directly correlated with specific functional activity. Hiippala and associates found that critical levels of platelets and clotting factors were not reached with blood loss and replacement until more than two estimated blood volumes had been replaced. However, fibrinogen deficits appeared much earlier.

DISSEMINATED INTRAVASCULAR COAGULATION

Disseminated intravascular coagulation is a disorder characterized by reduction in the elements involved in blood coagulation due to their utilization in widespread blood clotting within the vessels. It may be caused by a wide variety of disorders including hemorrhage, trauma, sepsis, toxic shock syndrome, aortic aneurysms, liver disease, peritoneovenous shunting, endotoxin release, abruptio placentae, and amniotic fluid embolism. (Table 24.1) (21).

The location and extent of trauma and the duration of shock are important factors in the development of disseminated intravascular coagulation (DIC) (2,22,23). DIC in the setting of massive transfusion is reported to occur in 5% to 30% of trauma patients and is associated with high morbidity and mortality rates of nearly 70% (4,18,24–27). In patients with blunt trauma, tissue injury may cause immediate activation of the clotting system. Tissue and cell fragments enter the blood stream, which in the presence of hypoperfusion and circulatory stasis induced by hemorrhage, result in severe DIC. In the patient with severe burns, both hemolysis and tissue necrosis release tissue components, cellular enzymes, and lipidlike material into the circulation, triggering DIC. Tissue thromboplastins liberated from brain tissue are a common but frequently underrecognized cause of DIC after head trauma (28). Acidosis-induced endothelial sloughing may also cause activation of the intrinsic clotting cascade (29).

Both the etiology and the progression of DIC are multifactorial and are characterized by defects in the antithrombin and tissue factor inhibitor pathways and the protein C system. Release of tissue factor (TF) from endothelial cells or other circulating cells is the most common initiating event. If natural inhibitors are abundant and if the causative agent or disease is corrected, DIC may be halted in a compensated state. Persistence of the triggering agent, e.g., a septic locus, leads to a *consumption coagulopathy* with loss of

TABLE 24.1
CAUSES OF DIFFUSE INTRAVASCULAR COAGULOPATHY (DIC)

- Sepsis
  - Gram-negative bacteria
  - Gram-positive bacteria
- Viruses
- Hemolysis (massive)
  - Transfusion of incompatible blood
- Ischemia
- Hypotension
- Hypoperfusion
- Trauma
  - Brain injury
- Systemic Inflammatory Response Syndrome (SIRS)
- Obstetrical emergencies
  - Abruptio placentae
  - Amniotic fluid embolism
  - Pre-eclampsia
- Snake bite
- Localized DIC
  - Aneurysms
  - Hemangiomas
- Allograft rejection
- Glomerulonephritis
- Malignancy
  - Prostate cancer
  - Acute promyelocytic leukemia

fibrinogen and platelets and the potential for diffuse bleeding. Failure the fibrinolytic system permits deposition of microvascular fibrin and MSOF (30).

Vervloet and colleagues at the University Hospital in Amsterdam, the Netherlands, are proponents of the theory that DIC is an imbalance between coagulation and fibrinolysis mediated by various cytokines and caused by increased levels of plasminogen activator inhibitor type 1 (PAI-1). Increased levels of PAI-1 produce a procoagulant state characterized by thrombin generation in excess of plasmin and impaired fibrin degradation, leading to widespread fibrin deposition. Thrombin generation proceeds via the extrinsic tissue factor/factor VIIa route at the same time as consumption of the natural coagulation inhibitors antithrombin III, protein C, and protein S increases. Although levels of plasminogen activator antigen are increased, its activity is almost completely inhibited by PAI-1. High plasma levels of thrombin–antithrombin complex (TAT) can be found.

The Amsterdam investigators have found that increased levels of PAI-1 are associated with poorer outcome and increased severity of multiple organ failure in patients with DIC from sepsis as well as other causes. Hardaway and Vasquez (32) believe that DIC may be initiated by release of a thrombogenic aminophospholipid from dying tissue or bacterial cells. Coagulation abnormalities secondary to DIC are coupled to the inflammatory response, which aggravates vascular permeability, inflammation, and cell damage in tissues. This combination of events leads to multiple system organ failure (MSOF) and death. DIC may produce adult respiratory distress syndrome through the mechanism of intravascular fibrin formation, vessel occlusion, and localized hypoxia (33).

Watanabe et al. (34) in Japan measured plasma levels of thrombin-activated fibrinolysis inhibitor (TAFI) activity and antigen in patients with DIC in a study designed to examine the role of hypofibrinolysis in this disorder.

Both TAFI activity and antigen levels were significantly below normal in patients with DIC. Decreases in TAFI were inversely correlated with increases in plasma thrombin–antithrombin III complex (TAT) and D-dimer, suggesting that thrombin generation and consumption of coagulation factors reduce TAFI. TAFI levels were not correlated with fibrinogen, plasma-alpha2 plasmin inhibitor complex (PPIC), and tissue type plasminogen activator/plasminogen activator inhibitor-1 (tPA/PAI-1) complex levels, supporting a role for TAFI as a secondary modulator of fibrinolysis.

Regardless of the inciting etiologic mechanism, the development of microvascular thrombosis plays an active role in major organ system failure including renal failure, gangrene, hepatic failure, and acute respiratory distress syndrome. Extensive activation of the coagulation system is almost always accompanied by concomitant activation of the fibrinolytic cascade. Consequently, both microthrombi and hemorrhage may be seen.

The development of DIC in the setting of hypothermia is multifactorial. Platelet dysfunction resulting from temperature-dependent diminished thromboxane B2 production causes a delay in platelet plug formation (35). Fibrin clot formation is also delayed because the enzymes of the coagulation cascade are temperature-dependent. Finally, large amounts of tissue thromboplastins resulting from tissue damage are released into the systemic circulation (28) and activate the extrinsic clotting cascade. Thus, DIC is frequently seen during cold ischemia, and not surprisingly, has been noted in hypothermic patients after rewarming (36,37).

Epidemiology

The incidence, clinical presentation and underlying disorders associated with DIC were examined in a series of 1,882 patients by Okajima et al. (38); 204 patients were diagnosed as suffering from DIC for an overall incidence of 10.8%. Malignancies led the list of underlying disorders with 33.8% of patients having solid tumors and 12.7% having hematological malignancies. Patients with aortic aneurysm (10.8%), infections (6.4%), unspecified postoperative complications (4.4%), liver disease (2.9%), obstetric disorders (2.5%), and miscellaneous diseases (26.5%) completed the diverse list. Clinical manifestations of DIC patients varied depending on underlying disease. The large majority of patients with either aortic aneurysm (95.5%) or postoperative complications (88.9%) had no clinical signs of DIC. Bleeding was observed in all obstetrical patients and in 32% to 50.0% of patients with liver disease, hematological malignancies, and solid tumors. Organ failure was observed in up to 33.3% of DIC patients with liver disease, hematological malignancies, and solid tumors. Although all of the patients with obstetric disorders had bleeding, only 20.0% of the patients had organ failure. In contrast, although only 15.4% of the patients with infections had bleeding, 76.9% of these patients had organ failure.

Chuansumrit et al. (39) at Mahidol University in Bangkok, Thailand, found a similar broad spectrum of underlying diseases in 100 pediatric patients with DIC. Of those 100, 45 patients were neonates with a mean age of 12.6 days and 55 patients were infants, children, and adolescents with a mean age of 6 years and 3 months. Most of them (91.5%) had complicated underlying conditions, which included congenital anomalies, prematurity, malignancy, hematological, and various diseases. The most commonly found initiator of DIC was gram-negative septicemia. Bleeding and thromboembolic events were found in 59.4% and 19.8%, respectively. Asakura et al. (40) examined the relationship between fibrinolytic enhancement and the

development of multiple system organ failure (MSOF) in 69 patients with DIC. Patients with both DIC and MSOF had higher levels of tissue plasminogen activator antigen (t-PA) and plasminogen activator inhibitor antigen (PAI), and more depressed levels of plasmin alpha2 plasmin inhibitor complex (PPIC) and fibrin/fibrinogen degradation products than those without MSOF. Thrombin-antithrombin complex (TAT) levels were similar in both groups. Thirty-eight patients without MSOF recovered from DIC, but only 14 of 31 patients with both DIC and MSOF survived. This latter group had significant increases in both t-PA and PAI-1, suggesting a role for these substances as prognostic markers. The authors concluded that enhanced fibrinolysis was an important defense mechanism in preventing the development of MSOF in DIC (40).

Diagnosis

The diagnosis of DIC is based on both clinical suspicion of DIC and a combination of laboratory tests. Patients with known underlying causes should be watched carefully for any indications of the development of DIC, such as evidence of microthrombi and/or bleeding. Evidence of ongoing consumption of coagulation proteins from laboratory testing includes decreasing fibrinogen levels and platelet counts. The laboratory abnormalities and clinical manifestations in DIC reflect consumption of clotting elements and enhanced fibrinolysis (Table 24.2). The combination of D-dimer and fibrin degradation products (FDP) provides a rapid and specific test. Serial FDP measurements may be used to follow the clinical course and AT to measure the severity and estimate prognosis (41,42).

Fibrin degradation products (FDP), or D-dimers, are frequently elevated in acute DIC, but are not diagnostic of DIC. FDP represent the biodegradation products of the action of plasmin on fibrinogen and fibrin. D-dimers are end products of the action of plasmin on fibrin and may be elevated in the absence of DIC. Platelet factor 4 and beta-thromboglobulin are elevated in DIC, but neither of these tests are diagnostic of DIC since they may be elevated in a variety of intravascular coagulation disorders. The irreversible complexing of some activated clotting factors (thrombin) with antithrombin III (AT III) leads to a significant decrease in functional AT III activity in acute DIC. Assessment of tissue plasminogen activator antigen concentration and activity may also be helpful in the diagnosis of DIC (32). With the exception of the FDP and D-dimer assays, laboratory turnaround time in the massively bleeding patient is unacceptably long for most of these other assays.

TABLE 24.2

LABORATORY ABNORMALITIES IN DIFFUSE INTRAVASCULAR COAGULOPATHY

Decreased platelets
Decreased fibrinogen
Decreased prothrombin
Decreased levels of factors V, VIII, XIII
Increased fibrin degradation products
Fibrin D-dimers

Molecular markers of in vivo hemostasis activation, such as thrombin–antithrombin (TAT) complexes, prothrombin fragment 1 + 2 (F 1 + 2), or plasmin-antiplasmin (PAP) complexes as well as increasing plasma levels of D-dimer, fibrin(ogen) split products (FSP), and soluble fibrin monomer (FM) are found as DIC progresses. FM elevations suggest the presence of thrombin while an increase in FSP confirms the generation of plasmin. Elevated D-dimer levels reflect both thrombin and plasmin production. It is necessary to repeat these studies both to make the diagnosis of DIC and to monitor therapeutic progress (43). Circulating factors can be used as markers of prognosis in DIC. Kotajima et al. (44) showed that plasma thrombomodulin [TM], a high-affinity thrombin receptor on vascular endothelial cells, was significantly higher in nonsurvivors of DIC compared to survivors (TM 3.1 +/− 1.52 versus 8.1 +/− 3.89 FU per ml) (45).

Laboratory testing and the interpretation of laboratory results in the diagnosis of dilutional coagulopathy and DIC in the massive transfused patient remain controversial. In some trauma patients, the clinical observation of a coagulopathy may not be confirmed by abnormal coagulation (PT and aPTT) tests (46). Rohrer and Natale (47) have shown progressive prolongation of coagulation tests (PT and aPTT) with varying levels of hypothermia. Because coagulation testing is routinely performed at 37°C, rather than at the patient's actual in vivo temperature, it is not surprising that normal coagulation tests can be obtained. Although these coagulation tests do not reflect in vivo clotting activity, normal test results do indicate that sufficient clotting factors are available for coagulation if normothermia is restored. On the other hand, coagulation tests may be normal or variably prolonged in the absence of microvascular hemorrhage. In addition, moderate to severe thrombocytopenia may be seen in acute DIC as well as dilutional coagulopathies (4).

Many investigators believe the laboratory diagnosis of DIC must demonstrate the action of thrombin on the fibrinogen molecule. Thrombin leaves the carboxyl terminals on the alpha and beta fibrinogen chains producing fibrin monomers and fibrinopeptides A and B. The detection of soluble monomer complexes by hemagglutination

technique is a rapid (20 minutes) and specific test to detect activation of thrombin. Although the determination of fibrinopeptide A is sensitive and accurate, the turnaround is unacceptably long (2 hours) in trauma-related microvascular hemorrhage. At the present time no single laboratory test can be used to confirm or exclude the diagnosis of DIC. However the combination of a low platelet count, a low fibrinogen, an elevated D-dimer, and the presence of soluble fibrin monomers in the context of the patients underlying condition are the most helpful indicators of DIC.

Treatment

In the past, the loss of coagulation factors and platelets were made up to a limited extent by the replacement of whole blood or by modified whole blood (4). Modified whole blood is prepared by resuspending red cells in the donor's plasma after platelet concentrates and cryoprecipitates have been removed. It differs from fresh whole blood in that only 15% of platelets, 40% of the factor VIII, and about 75% of the fibrinogen are retained in the product (17). Current treatment of DIC can be divided into three components: (a) Treatment of the underlying disorder, (b) Supportive management of bleeding complications, and (c) Treatment aimed at the coagulation process. It is imperative to treat the triggering underlying disease aggressively. This may require surgical drainage of an abscess or necrotic tissue, antibiotic therapy, control of temperature, volume replacement, and so on. Early recognition and early treatment of DIC are the keys to success, so a high index of suspicion must be maintained.

Continued DIC is characterized by a consumption coagulopathy of platelets. Ongoing bleeding or rapid hemorrhage may lead to anemia. These deficiencies can be corrected by administration of platelet concentrates and red cell transfusions if needed. Treatment should be aimed at correction of the patient's clinical condition, not at a measured deficit. Red cell transfusions may increase the fibrin deposition in DIC, so they should be used with caution.

Heparin has been used as the mainstay of treatment of DIC for over 30 years with little evidence of benefit. Based on animal studies, heparin is thought to control or stop the process of activated hemostasis system (12). However, a retrospective analysis of clinical use of heparin showed no evidence to support its routine use (43). Heparin may be most helpful in those patients with clinical manifestations of thrombosis, e.g., deep vein thrombosis. A trial of low molecular weight dalteparin compared to unfractionated heparin showed less bleeding and better organ system scores, but no survival benefit (48). The administration of concentrates of natural anticoagulants, i.e., antithrombin, protein C, or tissue factor pathway inhibitor is safer than heparins since they do not exacerbate the bleeding tendency. These concentrates were found to be effective in animal models of DIC but human experience is still limited. Generally, the earlier treatment is initiated, the better the patient's prognosis.

Restoration of defective coagulation pathways by administration of coagulation inhibitor concentrates or recombinant anticoagulant factors is associated with an improved outcome in experimental and (initial) clinical studies (49,50).

Early treatment of septic and traumatic shock with plasminogen activator has helped prevent the development of DIC in both animal models and humans (51). Results of the recent PROWESS [Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis] study of recombinant human activated protein C in 1,690 randomized patients with severe sepsis showed promise for the treatment of DIC. The mortality rate was 30.8% in the placebo group and 24.7% in the treatment group. This translates into a reduction in the relative risk of death of 19.4% (95% confidence interval, 6.6 to 30.5) and an absolute reduction in the risk of death of 6.1% ($P = 0.005$). However, the incidence of serious bleeding was higher in the treatment group than in the placebo group, approaching statistical significance (3.5% versus 2.0%, $P = 0.06$) (52). The utility of Antithrombin-III treatment for DIC is as yet unknown. A meta-analysis of 122 patients included in three placebo-controlled, randomized studies of Antithrombin-III (AT) therapy for severe sepsis showed a 22% reduction in the 30-day all-cause mortality and a reduction in the length of stay in the intensive care unit in the AT treated group. Although AT treatment significantly decreased the risk of death in one study, in the aggregate these results were not statistically significant (53). A Phase II trail of 210 patients comparing placebo and infusions of tissue factor pathway inhibitor (TFPI) showed a trend toward better survival at 28 days (54,55).

These trials of coagulation inhibitors have been conducted in patients with sepsis, not DIC, per se. Although they may be proven to play an important role in selected subgroups of patients, their efficacy and safety remain to be proven (56,57).

INDICATIONS FOR REPLACEMENT OF HEMOSTATIC FACTORS AND BLOOD PRODUCTS

In the trauma patient, the clinical and laboratory distinction between microvascular hemorrhage due to a dilutional coagulopathy and DIC may be extremely difficult. Nevertheless, every attempt should be made to determine the patient's coagulation status with appropriately selected blood tests and replace components to correct specific

TABLE 24.3
GUIDELINES FOR COMPONENT THERAPY IN MASSIVE TRANSFUSION

Component	Indications
Platelets	Platelet count $<$ 80–100 $\times$ 10^9/L
Fresh frozen plasma (FFP)	PT and/or aPTT $>$ 0.5 times normal
Cryoprecpitate and AHP	Fibrinogen $<$ 10 g/L

abnormalities. Practically speaking, because time is of the essence, the decision to administer component therapy to trauma patients with microvascular hemorrhage is often made prior to availability of laboratory results (Table 24.3). The location and extent of injury, the duration of shock, the response to resuscitation and the risk of complicating factors such as intracranial bleeding are important clinical considerations. With prompt management of bleeding, debridement of devitalized tissue, and the skilled use of component therapy, the coagulopathy can usually be controlled.

In the patient with microvascular hemorrhage, general thresholds for component replacement are as follows: transfuse platelets when the count is less than 80 to 100 $\times$ 109/L, FFP when the PT and/or aPTT are greater than one-and-a-half times normal, and cryoprecipitate when the fibrinogen is less than 10 g per L. The prophylactic administration of platelets in the absence of microvascular bleeding is controversial (4,5,58). Some investigators advocate prophylactic administration of platelets into patients with severe blunt trauma and thrombocytopenia because microvascular bleeding may be occult and because precious time and blood is lost if platelets are deferred until bleeding has become a problem (4,58). Hakala and colleagues used pure component therapy successfully in 18 of 23 patients who received more than 50 units of blood transfusion. Overall survival in this group was 70%.

Empirical replacement using a standardized regimen of platelet concentrates and fresh frozen plasma that depends on the amount of blood loss cannot be justified. This results in over transfusion in many patients with accompanying increased risk of disease transmission, and may exhaust available supplies of components. Further, such regimens frequently underestimate transfusion needs in patients who truly need blood products, especially those with a consumptive coagulopathy. Every effort should be made to restrict red blood cell transfusion unless there is a demonstrated clinical need. Stored red cells are poor oxygen carriers and increase cytokine load, possibly leading to progression of the coagulopathic process. Asanguineous fluids including crystalloids and colloids should be used initially to restore volume.

Recombinant Factor VIIa (rFVIIa) is a recent addition to the potential armamentarium of treatment options for DIC. Although the drug is not approved for use in this setting at present, several investigators have reported using rFVIIa in coagulopathic patients. Data from the NovoNordisk investigators' database showed that bleeding stopped or decreased in 32 of 40 (80%) patients who received rFVIIa for uncontrolled bleeding (60). Blood product usage was significantly decreased. However, mortality was high with over one half of treated patients dying [23 of 40 (57.5%)]. Early use of rFVIIa may be necessary to see any benefit. Clark et al. (61) used rFVIIa as a last ditch treatment in 10 of 50 patients who had been transfused with more than 10 units of packed red cells. Although they saw transient cessation or reduction of bleeding in 60% of patients, rFVIIa treatment did not improve survival.

COMPLICATIONS OF MASSIVE TRANSFUSION

Blood transfusion has the potential to produce both immediate and delayed adverse complications in as many as 10% of recipients; massive transfusion magnifies these risks. The trauma victim that survives the initial injury may succumb to delayed consequences of the resuscitative efforts including a delayed hemolytic transfusion reaction. Transfusion-related acute lung injury, transmitted disease, systemic inflammatory response syndrome, and an increased risk of serious, nosocomial infection (54–56,62–64). These complications are discussed in detail elsewhere in this text. Massive transfusion can cause several metabolic problems including citrate toxicity, hyperkalemia, acidosis, a shift in the oxygen-dissociation curve, and abdominal compartment syndrome. Since these risks are directly related to the number of donor exposures, the indiscriminate or prophylactic use of blood products is not warranted (65–67).

ABO-incompatible hemolytic transfusion reactions are the most common cause of acute fatalities from blood transfusion and are frequently the result of human error in patient or specimen identification occurring during situations of high emotion (68–69). Acute hemolytic reactions are usually caused by naturally occurring isoagglutinins (anti-A or anti-B), which activate complement and result in membrane lysis and liberation of free hemoglobin within the vascular system. The clinical response depends on the quantity of donor red cells, antigen specificity, immunoglobulin type (IgM versus IgG), antibody subclass, antibody thermal amplitude, antibody titer, and the clinical condition of the recipient (38). The complex interaction of the complement system, the kallikrein–kinin system, the coagulation system, and the neuro-endocrine system

account for the often catastrophic clinical findings of acute hemolysis due to ABO incompatibility; namely, acute renal failure, DIC, and death. A hemolytic reaction in a critically injured or massively transfused patient may be overlooked. Clinical findings of hemoglobinuria, hypotension, fever, and microvascular hemorrhage may be attributed to traumatic injury. Use of type-specific blood helps avoid these delayed reactions, as does utmost care in preventing clerical error through correct patient identification.

To ensure the complete anticoagulation of blood, excess citrate is used to bind calcium and prevent clotting. The citrate load administered during massive transfusion depends on the plasma volume of the blood products administered. CPDA-1 and Adsol red cell concentrates contain 5 mg per mL and 2 mg per mL of citrate, respectively. However, the plasma from Adsol units contains nearly 30 mg per ml of citrate from the CPD anticoagulant used in the initial collection (70). Therefore during massive transfusion, the plasma-containing blood products (FFP, platelets) are the major source of citrate. Citrate is excreted in the urine and metabolized rapidly by the liver in normal patients. The end product of its metabolism is bicarbonate. Normal calcium levels are restored by mobilization of skeletal calcium stores. Citrate infusion causes a transient decrease in ionized calcium. However, in patients who have limited ability to metabolize citrate, particularly those with severe hypotension, hypothermia, hepatic injury, or preexisting hepatic disease, citrate toxicity can cause muscle tremors, increased myocardial irritability, and decreased cardiac output (48). Irreversible ventricular fibrillation may occur at citrate levels of 60 m per mL. The use of calcium salts should be reserved for selected massively transfused patients with clinical manifestations of citrate toxicity.

Hyperkalemia

Potassium is known to leak from red blood cells during storage. Although the extracellular potassium concentration of AS-1 RBC at 42 days is approximately 60 to 70 mmol per L, the actual potassium content is 7.5 mmol per unit. This metabolic load is transient, as potassium reenters red cells within a few hours after transfusion. In actual practice, patients may experience a paradoxical hypokalemia resulting from the metabolism of citrate to bicarbonate and increased urinary excretion of potassium (14,71). In clinical practice hyperkalemia may occur during rapid blood transfusion in patients with severe shock or renal dysfunction, and in patients with extensive muscle necrosis. In recent years, the ability to infuse large volumes of stored blood rapidly using high capacity blood warmers has increased the risk of hyperkalemia in these patients (71). Since hyperkalemia and hypokalemia are associated with cardiac dysfunction, close monitoring of potassium levels is recommended in the massively transfused patient.

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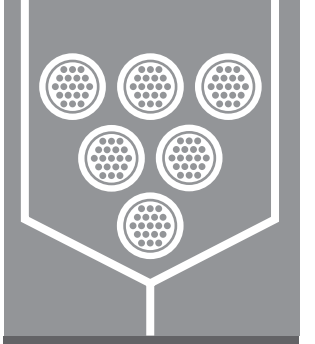
Coagulation Issues



25

Coagulation Product Use in the Perioperative Period

Richard K. Spence *Aryeh Shander*

Use of plasma and plasma-derived coagulation products has always involved a careful balance of anticipated benefit versus risk. Risk reduction through pathogen-inactivated products has been successful, but the expense of manufacture does not warrant widespread use. Although plasma has always had limited indications for use, these are often misunderstood or ignored in favor of received knowledge and tradition. Solid evidence from multiple trials support the limited indications for fresh frozen plasma (FFP) described here and support products that target specific coagulation defects.

CLINICAL USE OF PLASMA AND PLASMA FRACTIONS

Plasma and its derivatives are among the least understood and the most frequently misused of the three major blood components (1–3). This lack of understanding extends beyond knowledge of just what these products are to include when they should be used. This chapter addresses these issues from the viewpoint of clinicians with an interest in blood and blood product management.

Preparation and Products

The term *fresh frozen plasma* (FFP) may sound like an oxymoron, since the product cannot be both fresh and frozen. However, fresh refers to the collection of plasma within the time frame of blood donation and anticoagulation; frozen refers to its preservation state; so the name describes the collection process rather than the actual product. FFP is collected in two ways—by centrifugation of donated whole blood or by plasmapheresis. The volume of FFP collected varies and ranges from 150 mL to 400 mL. Once the plasma is collected, it is frozen rapidly to below −18°C within 8 hours and is stored at this temperature. Anticoagulants are shown on the product label and contain varying proportions of contain varying proportions of trisodium citrate, citric acid, sodium monophosphate, dextrose,and possibly adenine.

Plasma is available in several forms based on how the original material is processed and stored. Fresh frozen plasma as described above contains plasma proteins and coagulation factors. Plasma frozen within 24 hours of phlebotomy (PF24) refers to plasma that has been separated and stored at −18°C or less within 24 hours of whole blood collection. FFP donor retested is the same product that has been stored for 112 days until the donor has been retested and found negative for all required tests. The quarantine period helps eliminate the risk of viral transmission from donors who may have been in the infectious window period. Thawed plasma is FFP that has been collected and prepared in a closed system, thawed at 30°C to 37°C and stored at 1°C to 6°C for up to 5 days. Liquid plasma is separated from expired units of whole blood within 5 days and is refrigerated at 1°C to 6°C. FFP and PF24 are the products used most often.

FFP must be thawed and used immediately. It can be stored at 1°C to 6°C, or refrigerator temperatures, for up to

24 hours. Efficacy of thawed FFP is determined by the amount of coagulation factors present. By definition, each mL of undiluted plasma contains one international unit of the coagulation factor listed (4). An acceptable unit should have at least 70 IU per ml of Factor VIII. In general, units of FFP prepared from whole blood and from plasmapheresis are equivalent in terms of hemostatic ability. PF24 may have somewhat lower levels of FVIII than plasma frozen within 8 hours of collection but this reduction does not affect the clinical usefulness of FFP in the situations where FFP is indicated (5,6). Prestorage leuko-reduction may improve coagulation factor levels (7).

When FFP is thawed slowly at 1°C to 6°C , the cryoglobulins remain precipitated and can be separated from the supernatant by centrifugation and then refrozen within 1 hour. The cryoprecipitate is also known as Cryoprecipitate Anti-Hemophiliac Factor (AHF). Cryoprecipitate AHF may come from a single donor but most often comes from pooled donor plasma and is labeled Cryoprecipitate AHF-Pooled. Factors that precipitate in this process include FVIII, von Willebrand factor (VFW), FXIII, fibrinogen, and fibronectin. These cryoprecipitants are resuspended in a small volume of plasma for clinical use. An acceptable unit should have at least 70 IU per ml of Factor VIII and at least 140 mg of fibrinogen. Cryoprecipitate Reduced Plasma refers to the supernatant left after removal of the cryoprecipitate. Cryosupernatant is deficient in both FVIII and fibrinogen when compared to cryoprecipitate, although as much as 70% of the original fibrinogen may remain. Cryosupernatant also contains VWF metalloproteinase (5). Table 25.1 shows the primary plasma proteins and coagulation factors contained in the above products.

TABLE 25.1
PLASMA PROTEIN AND COAGULATION FACTOR CONTENTS OF PLASMA PRODUCTS

Product	Protein/Factors
FFP	All plasma proteins and both stable and labile coagulation factors
FFP Retested	All plasma proteins and both stable and labile coagulation factors
PF24	Same as FFP but reduced amounts of FVIII and FV
Thawed plasma	Same as FFP but reduced amounts of FVIII and FV
Liquid plasma	Same as FFP but reduced amounts of FVIII and FV
Cryoprecipitate-AHF	Factors VIII, XIII, vWF, fibrinogen and fibronectin. Deficient in other plasma proteins
Cryoprecipitate Reduced Plasma	VWF metalloproteinase. Deficient in FVIII, vWF, fibrinogen, cryoglobulin and fibronectin

Risk

Plasma-derived blood components contain essentially the same risks of disease transmission as packed red blood cells and platelets. However, the risk is mathematically increased with pooled plasma products sourced from multiple donors. It is because of these risks and the inability to screen for all potential pathogens, e.g., the prion associated with new variant Creutzfeldt-Jakob disease that methods to reduce infectivity of plasma units have been pursued (8).

The risk of transfusion-transmitted disease (TTD) from plasma products prompted the development of blood products that are free of pathogens. Pathogen-inactivated plasma is produced with several methods including filtration, pasteurization, addition of a photosensitizer, e.g., methylene blue and light treatment (MBFFP) or by solvent detergent treatment (SDFFP) (9,10). Pasteurization (10 hours at 60°C) kills both enveloped and nonenveloped viruses while solvent detergent processing removes only the latter. Both pasteurization and solvent detergent treatment require the collection of pooled plasma from multiple donors (11).

Some controversy exists over the effect of these processes on plasma protein and coagulation factor survival. Beeck et al. (12) showed no reduction in fibrinogen, FV, FVII, and FVIII in SDFFP compared to standard FFP. However, others have shown reductions in several clotting factors and plasma proteinase inhibitors (13). Weiding et al. (14) found that pathogen inactivation processing reduced coagulation factors by roughly 5% to 20%. Solvent detergent treatment reduced protein S and alpha 2-antiplasmin by approximately 40%, whereas methylene blue (MB) treatment lead to a significant photo-oxidative alteration of fibrinogen with a disturbance of fibrin polymerization (14). Doyle et al. (15) found significant reductions in factor V (31%), factor VIII (28%), and protein S (50%) in SDFFP plasma. Suontaka et al. (16) showed that MB plus red light treatment affected the polymerization and gelation phase of fibrin, producing a tighter fibrin gel structure, but no effect on stabilization of fibrin clot or fibrinolysis was found. The comparison of outcomes and posttransfusion levels of coagulation factors in patients treated with either FFP or SDFFP by Beck et al. (17) showed no differences and no significant, clinical impact.

Although solvent detergent treated plasma adds a margin of safety, most feel that it is too small to justify the added production costs. Aubuchon and Birkmeyer (18) noted that compared with untreated plasma, a unit of SD FFP produces a net benefit of 35 minutes in quality-adjusted life expectancy at a cost of about $19. When they

extrapolated this to the 2.2 million plasma units transfused annually in the United States, SDFFP achieved a savings of 147 quality-adjusted life-years at a cost of $42.5 million. They concluded that the cost did not justify widespread use of SDFFP.

Plasma products carry risks other than TTD. All FFP units must be ABO compatible with the intended recipient to avoid reactions. In addition, FFP and its byproducts carry the risk of transfusion related acute lung injury (TRALI), which is thought to be caused by the donor and recipient plasma interactions of leukocyte alloantibodies and biologically active lipids. All plasma-containing blood products have been implicated in TRALI, including fresh frozen plasma (19). The estimated incidence of TRALI is 1:5000 transfused units with a mortality rate of up to 10% of cases (20).

CLINICAL USE OF FFP AND PLASMA PRODUCTS IN THE PERIOPERATIVE PATIENT: CURRENT RECOMMENDATIONS

The evidence-based indications for the use of fresh frozen plasma are few and specific. (Table 25.2) Reviews and published guidelines that evaluate the literature either for or against specific uses for plasma are fairly consistent in their findings that, with the exception of emergencies the use of plasma without laboratory analysis to verify a coagulopathy is not justified (21,22).

Single Factor Deficiencies

FFP may be used to treat *single* coagulation factor deficiencies perioperatively, if no safe individual factor replacement products are available and possible bleeding is anticipated. This typically occurs with Factor V and XI deficiencies. Lepatan et al. (23) have proposed the use of cryosupernatant in the treatment of Hemophilia B because of the high levels of Factor IX. However, FFP also may be used instead of Factor IX isolates if there are concerns about thrombogenicity caused by the latter. Hemophilia patients should be treated before, and throughout, the operative period to protect against unwanted bleeding. Guidelines are discussed in more detail in Chapter 30. Isolated laboratory abnormalities should not be treated.

Cryoprecipitate is indicated primarily for reversal of hypofibrinogenemia caused by massive transfusion or DIC. Of the 88 units of cryoprecipitate used in 51 patients reported in Pantanowitz and Kruskall's (24) recent review, 10 (20%) were used in the manufacture of fibrin sealant. Occasional uses included the reversal of tissue plasminogen activator (n = 1) and correction of uremic bleeding (n = 2). Unfortunately, 24% of all cryoprecipitate orders were inappropriate. Cryoprecipitate should be considered the second line of defense in the treatment of von Willebrand's disease, Hemophilia A, and Factor XIII deficiency when virus-inactivated or recombinant products are not available.

TABLE 25.2

GUIDELINES AND RECOMMENDATIONS FOR USE OF FFP AND PLASMA PRODUCTS

1. Single coagulation factor deficiencies if no safe, individual factor replacement products are available.
2. Multiple coagulation factor deficiencies with severe bleeding in DIC.
3. TTP.
4. Reversal of warfarin effect.
5. Surgical bleeding and hemostasis.
6. Hemorrhagic disease of the newborn.
7. Neonates with coagulopathy, risk of bleeding and need for surgical procedure.
8. Red cell T antigen activation in newborns.

Multiple Factor Deficiencies/DIC

FFP is indicated in the treatment of *multiple* coagulation factor deficiencies with severe bleeding such as those seen with disseminated intravascular coagulation (DIC) if specific factor replacement has failed. Restoration of defective coagulation pathways by administration of specific factor replacements, e.g., cryoprecipitate for fibrinogen deficiency, coagulation inhibitor concentrates, or recombinant anticoagulant factors should be tried first, since these are associated with an improved outcome in experimental and (initial) clinical studies (25–27). Cryoprecipitate is used most often in patients with acquired fibrinogen deficits following massive transfusion and DIC. Early treatment of septic and traumatic shock with plasminogen activator has helped prevent the development of DIC in both animal models and humans (26). Results of the recent PROWESS [Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis] study of recombinant human activated protein C in 1,690 randomized patients with severe sepsis showed promise for the treatment of DIC. The mortality rate was 30.8% in the placebo group and 24.7% in the treatment group. This translates into a reduction in the relative risk of death of 19.4% (95% confidence interval, 6.6 to 30.5) and an absolute reduction in the risk of death of 6.1% (P = 0.005). However, the incidence of serious bleeding was higher in the treatment group than in the placebo group, approaching statistical significance (3.5% versus 2.0%, P = 0.06) (26).

The utility of Antithrombin-III treatment for DIC is as yet unknown. A meta-analysis of 122 patients included

in three placebo-controlled randomized studies of Antithrombin-III (ATIII) therapy for severe sepsis showed a 22% reduction in the 30-day all-cause mortality and a reduction in the length of stay in the intensive care unit in the AT treated group (28). Although ATIII treatment significantly decreased the risk of death in one study; in the aggregate these results were not statistically significant.

These trials of coagulation inhibitors have been conducted in patients with sepsis, not DIC, per se. Although they may be proven to play an important role in selected subgroups of patients, their efficacy and safety in the perioperative period remain to be proven (29–31).

Trauma

Coagulopathy is a frequent finding in the trauma patient and may be caused by a combination of events including dilution of clotting factors and platelets following transfusion, hypothermia, and disseminated intravascular coagulation (32–34). Dilutional coagulopathy may occur, depending upon the amount of blood lost and transfused. Nearly 37% of the original blood elements remain in circulation following the controlled exchange of a single blood volume (10 units in a 70 kg adult). Remaining levels of coagulation factors and platelets (>100,000) are usually adequate to maintain hemostasis. With progressive exchanges of two volumes (equivalent to a 20 unit transfusion), blood elements drop to levels of approximately 5%, and coagulopathy follows (27). Microvascular bleeding may be associated with coagulopathy when PT or APTT values exceed one-and-a-half times mean controls and/or when fibrinogen levels fall below 1.0 g per L.

However, the role of FFP in this setting is unclear as are both the timing and the amount of FFP needed. Ledgerwood and Lucas (38) followed 22 patients admitted with hemorrhagic shock for up to 26 days to determine the role of FFP resuscitation in correcting coagulopathy. Hemorrhagic shock led to significant reductions in fibrinogen (factor I), factor V, and factor VIII that returned to normal over 1 to 26 days. Clotting times mirrored fibrinogen, factor V, and factor VIII levels. Their patients received an average of 21 units of packed red blood cells, 16.5 L crystalloid solution, and 1.25 L of FFP during surgery for control of bleeding. Mixed results with bleeding control in these patients along with information gained from animal studies prompted them to use FFP early in resuscitation to maintain coagulation proteins.

One ml of FFP per kilogram of patient weight will raise most clotting factors by approximately 1%. Hellstern and Haubelt (13) state that repeated, rapid infusions of 10 to 15 mL of FFP per kg of body weight will be required to raise clotting factor levels significantly and to achieve adequate hemostasis. de Jonge (30) advises that blood product support should be based on clinical judgment and must be guided by repeated laboratory tests of coagulation. He cautions that it is difficult to achieve hemostasis below critical coagulation factor levels, e.g., prothrombin time or activated partial thromboplastin time >1.8 or fibrinogen <1.0 g per L.

The above levels serve only as basic estimates in the clinical setting, since both platelet counts and amounts of circulating clotting factors will vary depending on both rate of blood loss and rate of transfusion. Guidelines for specific component therapy during massive transfusion in patients with clinical evidence of microvascular bleeding are shown in Table 25.3 (24,25). There is no place today for the use of cookbook formula that calls for the infusion of FFP after a predetermined number of units of packed RBCs has been transfused.

Although specific guidelines can be helpful in deciding when to use component therapy, they may also lead to under transfusion if the decision to transfuse is based only on laboratory values. Bleeding in trauma patients is often multifactorial and may not correlate directly to laboratory measurements. The turnaround time for obtaining laboratory results, and for readying plasma for transfusion, must be taken into particular consideration in cases of rapid blood loss (28). The location and extent of injury, the duration of shock, the response to resuscitation, and the risk of complicating factors such as intracranial bleeding are important clinical considerations. With prompt management of bleeding, debridement of devitalized tissue, and the skilled use of component therapy, the coagulopathy can usually be controlled.

Alternative approaches must be considered in situations where hemorrhage is uncontrollable despite blood component therapy. These include the use of other blood products such as prothrombin complex concentrates, fresh whole blood or fibrin glue, and pharmacological agents (e.g., desmopressin, aprotinin).

Surgical Bleeding and Hemostasis

Treatment of coagulopathy during or immediately after elective surgery should be treated in the same manner as DIC. Freeman et al. (35) reviewed the records of 260 patients

TABLE 25.3
GUIDELINES FOR COMPONENT THERAPY IN MASSIVE TRANSFUSION

Component	Indications
Fresh frozen plasma (FFP)	PT and/or aPTT >1.5 times normal
Cryoprecpitate and AHP	Fibrinogen <1.0 g/L

who underwent major hepatectomy between May 1997 and February 2001 for colorectal metastasis in an attempt to define a standard for FFP use in these patients(35). Eighty-three (32%) patients received a total of 405 units of FFP (median of four units). Most were transfused within the first two postoperative days after either right lobectomy or extended right lobectomy (34). Postoperative complications did not correlate with FFP use. The authors used an admittedly conservative criterion of a prothrombin time of 16 to 18 hours for transfusion. Their review of other centers showed that there was no universal trigger for FFP use. Freeman et al. (35) showed that FFP and SDFFP were equally effective in correcting coagulopathy in a randomized trial of 28 patients undergoing orthotopic liver transplantation (OLT).

Prophylactic use of FFP is not necessary in major liver surgery, as demonstrated by Jabbour et al. (36) in their report of live donor liver transplantation in eight Jehovah's Witness patients. Successful transplantation with 100% survival in this group was achieved using preoperative blood augmentation with erythropoietin, intraoperative cell salvage, and acute normovolemic hemodilution. A recent review of the use of alternatives to transfusion of blood and blood products describes how approaches such as Jabbour's can be successful in a wide variety of surgical procedures (36). Avoidance of coagulopathy through careful control of operative bleeding and the judicious use of antifibrinolytic agents such as aprotinin will avoid patient exposure to plasma products.

Coagulation test-based algorithms may reduce transfusion of non-erythrocyte allogeneic blood in patients with abnormal bleeding. Nuttall et al. (37) performed a prospective, randomized trial comparing allogeneic transfusion practices in 92 adult patients with abnormal bleeding after cardiopulmonary bypass. A control group was treated following an individual anesthesiologist's transfusion practices (TP); a protocol group was treated using a transfusion algorithm guided by coagulation tests (TA). The TA group received less fresh frozen plasma after bypass (median, 0 units; range, 0 to 7 units) than the TP group (median, 3 units; range, 0 to 10 units) ($P = 0.0002$). Postoperative mediastinal blood loss, overall ICU blood loss and the need for surgical reoperation of the mediastinum for bleeding were all significantly less in the TA group.

In the end, clinical judgment must prevail, even if this results in what appears to be overuse of components, based on laboratory measurements. Conversely, prophylactic or empiric transfusion of components using a cookbook approach without clinical evidence of bleeding should be avoided, since this depletes precious supplies and leads to increased risk of transfusion-related complications. One should, however, keep in mind the basic guidelines that there is no role for plasma products in restoring volume losses or for prophylactic administration of FFP in a patient who is not bleeding. The use of fresh whole blood when all else fails may have a role (38).

Thrombotic-Thrombocytopenic Purpura

Thrombotic-thrombocytopenic purpura (TTP) is a clinical syndrome characterized by neurological symptoms, fever, renal impairment, thrombocytopenia, hemolytic anemia, and microvascular thrombosis that results in variable degrees of tissue ischemia and infarction (39). Large vessel thrombosis is uncommon. The syndrome is associated with both familial and acquired factors but the initiating cause often goes undetected. Recent studies have shown a relationship between the actions of a vWF metalloprotease, ADAMTS13, and platelet adherence to the extracellular vascular matrix (40). ADAMTS13 (A Disintegrin And Metalloprotease with ThromboSpondin type 1 motif 13) is a plasma zinc metalloprotease that cleaves vWF in the process of coagulation. A deficiency of ADAMTS13 creates a propensity for increased vWF-platelet aggregation that results in the intravascular thrombosis seen in TTP (41). ADAMTS13 deficiency can be caused by a genetic mutation or the action of autoimmune inhibitors. Several drugs have been implicated in the development of inhibitors and clinical TTP including cyclosporine A, mitomycin-C, ticlopidine, simvastatin, Lipitor, and Plavix (42). Infection with the human immunodeficiency virus (HIV) has also been associated with TTP.

Approximately 80% of patients with TTP respond to plasma exchange therapy alone (43). Some patients undergo splenectomy or are treated with steroids, antiplatelet agents, and anti-metabolites such as vincristine, particularly those who relapse or fail treatment (44). Therapeutic plasma exchange with 40 ml FFP per kg of body weight is usually done in the perioperative period for surgical candidates (45). FFP replenishes the deficient ADAMTS13 while plasma exchange removes some of the pathogenic autoantibodies and endothelial-stimulating cytokines. Although plasma exchange using FFP has a good track record, it is unknown if this is the best exchange medium. Furthermore, there are no trials of either the appropriate volume or the duration of exchange therapy in TTP. McCarthy et al. (46) have treated over 160 patients using FFP, solvent detergent (SD) and cryosupernatant as the exchange media. They showed that SD plasma has value added in virtually eliminating all allergic reactions during treatment.

Preoperative Reversal of Warfarin Effect

Published guidelines recommend that fresh frozen plasma is indicated for urgent reversal of over-anticoagulation

from warfarin therapy with certain caveats (47). FFP is not indicated as primary therapy and is only partially effective because some units do not contain sufficient levels of factor II, factor VII, factor IX, and factor X to correct the coagulation defect (48). More specific agents such as prothrombin complex concentrate should be tried first if available (21). Correction of an abnormal PT, PTT, or INR should be done with either oral or parenteral Vitamin K in the absence of serious bleeding. Most importantly, FFP should not be used in the absence of associated, severe bleeding (47,48). Treatment must be monitored just as with other coagulopathies.

Vitamin K Deficiency

Simply stated, there is no evidence to support the use of FFP or other plasma products to treat Vitamin K deficiency (47). Either oral or parenteral Vitamin K is appropriate treatment.

Liver Disease and Elevated PT

Just as with treatment of Vitamin K deficiency, there no evidence of benefit gained from using FFP in patients with liver disease and an elevated PT (47,49). This holds true for patients treated in anticipation of a liver biopsy since studies evaluate correction of abnormal lab values, not clinical outcomes. No randomized trials of FFP versus no therapy in liver disease have been done. The few randomized trials of FFP have focused on comparisons of standard FFP to prothrombin complex concentrates or solvent-detergent preparations (50,51). Youssef et al. (51) recently reported their evaluation of the efficacy of FFP in correcting abnormal coagulation parameters in 20 patients with liver disease. The mean prothrombin time was numerically improved by the infusion of two to six units of fresh frozen plasma but only 10% to 12.5% of the patients had correction of their coagulopathy. Unfortunately, one patient had a complication from the FFP infusion, which highlights the risk of its use as opposed to its presumed benefit. Eleven consecutive patients randomized by French and colleagues (52) to receive either four units of FFP or five units of cryoprecipitate. Both products numerically improved the INR, aPTT, and fibrinogen concentration levels. Although the authors report that there were no differences in any of the other measured variables, one patient developed acute pulmonary edema while receiving FFP. Once again, the use of FFP and cryoprecipitate in the absence of clear clinical indications lead to increased risk.

Hemorrhagic Disease of the Newborn

Indications for FFP that are specific to the pediatric age group include hemorrhagic disease of the newborn with bleeding and extracorporeal membrane oxygenation. In the former, replacement therapy with highly specific factor concentrates should be used to avoid the high volume infusions associated with FFP. FFP as a replacement therapy is only indicated when no specific concentrate is available, as is the case in factor V deficiency and factor XI deficiency (53). There is no clear indication for prophylactic FFP to correct abnormal laboratory values prior to invasive procedures in healthy neonates and infants with no clinical evidence of abnormal hemostasis. Similarly, FFP is not indicated for prophylactic use in preventing intraventricular hemorrhage in preterm infants (54).

Pediatric Heart Surgery

Pediatric cardiac surgeons have traditionally used FFP as a pump prime for open heart surgery in infants and children. The value of FFP in this setting is controversial. Two separate groups conducted prospective randomized studies of small numbers of pediatric cardiac surgical patients to determine if the addition of FFP to the cardiac heart–lung machine prime had an impact on blood loss and transfusion need (55,56). Twenty infants weighing less than 8 kg studied by McCall et al. (55) received either 1 U of FFP (10 patients) or no FFP (10 patients) in the pump prime. The postbypass mean fibrinogen level was significantly higher in the FFP than the no FFP group (123 +/− 20 versus 58 +/− 17 mg per dL; $p < 0.0001$). The FFP group received significantly fewer units of cryoprecipitate (0.4 +/− 0.8 versus 2.0 +/− 0.9 U per patient; $p < 0.001$), and had a mean total donor exposure of 4.1 +/− 1.5 U per patient versus 5.4 +/− 1.4 U per patient in the no FFP group ($p = 0.06$). The authors concluded that the use of FFP in the pump prime significantly limited dilutional hypofibrinogenemia, decreased the transfusion of cryoprecipitate after bypass, and tended to decrease the overall mean patient exposure to blood products

Anesthesiologists at the Mayo Clinic found the opposite in their prospective randomized study of 56 patients weighing 10 kg or less who receive either one unit of fresh frozen plasma or 200 mL of albumin 5% in the cardiac bypass prime (56). Blood loss during the first 24 hours was similar in both groups, but total transfusions were significantly greater in those who received FFP versus albumin 5% in the prime (8.0 +/− 4.2 versus 6.1 +/− 4.5 U, respectively; $p = 0.035$). However, the addition of FFP to the prime in cyanotic patients and those undergoing complex operations resulted in less blood loss than albumin 5%. The authors concluded that the use of albumin 5% instead of fresh frozen plasma in the prime of acyanotic patients significantly reduces perioperative transfusions without increasing blood loss. The small numbers in both studies and the mixed results based in part on the presurgical status

of the patient leaves us without solid evidence-based support to recommend the use of FFP in pediatric cardiac bypass prime.

Volume Resuscitation

Controversy exists over which fluids to give bleeding patients and extends to the decision of how early and much resuscitation is needed. Proponents of colloids, including FFP and human albumin, claim that the greater intravascular persistence of these products makes them better resuscitation fluids than crystalloid solutions. Several reviews of crystalloid versus colloid trials have all concluded that there is no advantage to using plasma-derived products. Stanworth et al. (57) concluded from their systematic appraisal of 57 randomized trials involving fresh frozen plasma (FFP) that there was little evidence for the effectiveness of the prophylactic use of FFP. Most trials were limited by small numbers of patients and inadequate information on outcomes and the extent to which adverse effects might negate the clinical benefits of treatment with FFP. Roberts et al. (58) reviewed 19 randomized trials that compared colloid to crystalloid fluid administration in critically ill patients. They found no significant evidence that resuscitation with colloids decreased mortality in trauma, burn and surgical patients. A separate review of the role of colloids in fluid resuscitation compared outcomes of trials using FFP, albumin, gelatins, and hydroxyethyl starch solutions (59). Evidence showed that one colloid solution was no better than another. A logical conclusion is that if asanguineous and blood product-derived colloids, i.e., FFP, are comparable, use of the latter only adds unwarranted risk during resuscitation. This is underscored by the findings of another Cochrane Database Review of the use of human albumin versus crystalloids in volume expansion (60). The overall risk of death with albumin treatment was 14% compared to 8% in the crystalloid group.

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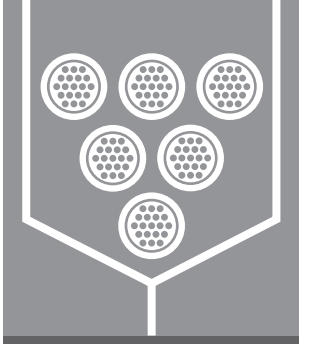


26

Perioperative Coagulation Monitoring

Linda Shore-Lesserson *Bruce D. Spiess*

The mechanisms of coagulation and hemostasis are reviewed in Chapter 7. Some concepts from that chapter are repeated in the current chapter in order to frame the context of rational hemostasis monitoring in the preoperative and perioperative period. The data and concepts of coagulation function have changed radically over the last 10 years. Unfortunately, the available clinical coagulation monitoring devices have not changed as radically, although there are now some schemes and algorithms that may be incorporating some of these changes (1). This chapter discusses hemostasis as an event occurring at the site of endothelial injury or dysfunction. It examines the limitations placed on our monitoring and the individual tests available. Finally, it suggests combining those tests in the most appropriate way to guide rational therapy. The appropriate utilization of testing is to test for the most likely hemostasis abnormalities early and treat them first; subsequent testing may test for less likely abnormalities.

REVIEW OF THE CONCEPT OF COAGULATION

Hemostasis is the body's normal response to vascular injury and involves a complex interplay of systems within the body that helps to seal the endovascular defect (2,3) and prevent exsanguinations (4,5). Blood is maintained in a liquid form by an active process involving plasma proteins (alpha-2-antitrypsin, antithrombin III, other antithrombins), prostaglandins (E_1), heparan, proteins C and S with thrombomodulin, tissue plasminogen activator, nitric oxide, and proteoglycan (6–9). There may well be a number of other inducible compounds that are antithrombotic as well. Many of these are produced by endothelial cells to maintain blood in its liquid form. Damage to the endothelial cell leads to a loss of the protective feedback mechanisms that cause cessation of coagulation. Unfortunately, we have no method of assessing local endothelial cell function. Coagulation is an event that occurs at a site of endothelial injury, however the changes that occur at the site of injury are diluted in the circulating blood volume. The concentration of proteins and cell lines change as they are produced and consumed and monitoring technology may be unable to measure the concentrations accurately. Another limitation of coagulation monitoring is that it is not a dynamic monitor. It is reflective of only a snapshot in time. A blood sample is obtained at a specific time, and to date we do not have continuous monitoring devices such as we have for hemodynamics. Also, the coagulation data require some time to acquire. For many of the coagulation tests, that amount of time required for data acquisition has become a limiting factor in their utility. Timely and rapid data acquisition is an important requirement for hemostasis testing. Attempts have been made to increase the speed of data acquisition, and on-site coagulation analyzers now exist that can provide bedside testing and interpretable results in a matter of minutes (1,10–12). Other systems improvements allow routine laboratories to control the testing and provide timely data. The present-day limitations to testing speed should therefore rarely provide such

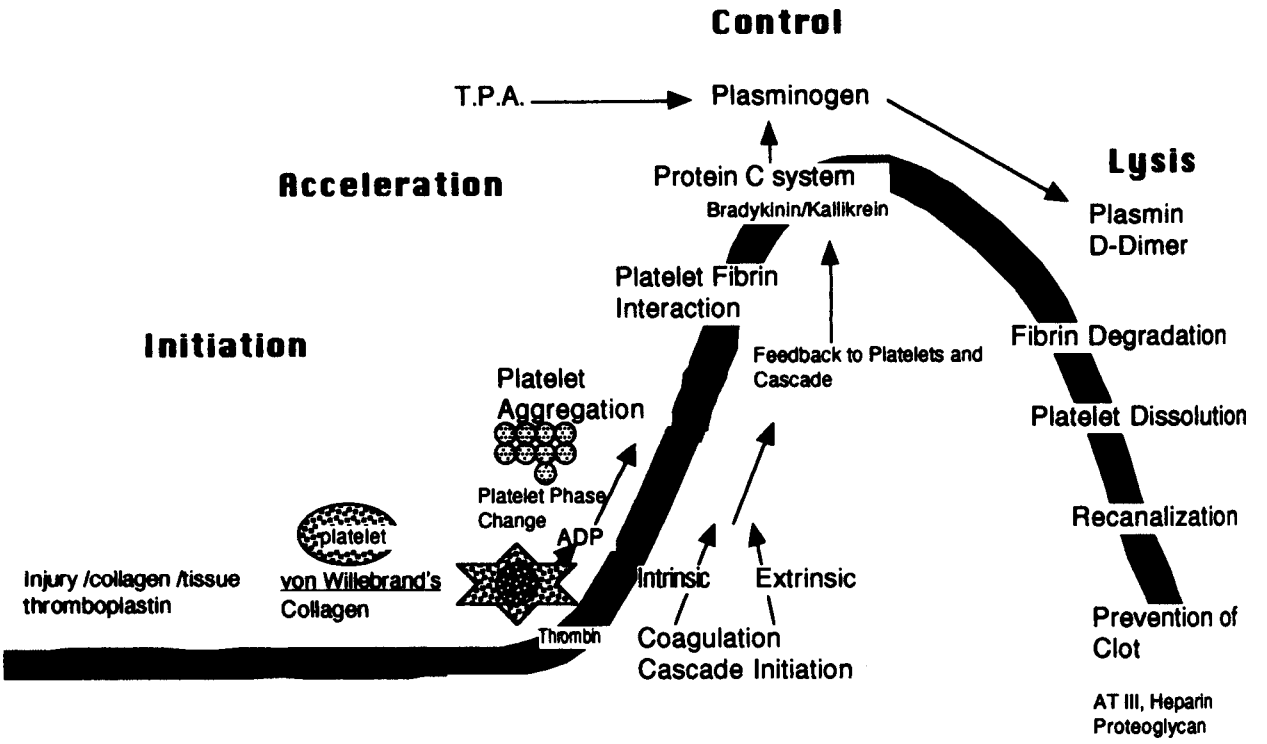


Figure 26.1 The coagulation events are limited to a localized area of dysfunctional endothelium. The events occur as a wave of activity brought on by activation, furthered by acceleration, limited by control, and eventually leading to lysis. (Reprinted by permission from Spiess BD. Perioperative coagulation concerns: function, monitoring and therapy. *Clin Anesth Updates.* 1993;4:1–6.)

an impediment that clinical judgment is necessary to treat a coagulopathy.

Coagulation is a complex array of systems that occur at the site of the blood and endothelial interface (Fig. 26.1). Coagulation is triggered by the injured endothelium. The endothelium loses its local anticoagulant potential and allows exposed collagen or basement membrane to further activate clotting. Extravascular tissue destruction will lead to tissue thromboplastin (tissue factor) release, and endothelial cells can be triggered to increase RNA encoding and production of their own tissue factor (6). This early phase of coagulation can be thought of as an activation phase.

Once the initiation phase has occurred, there is a rapid movement to the acceleration phase, where platelets play a vital role. Platelets are activated by exposure to collagen, tissue factor, and other agents released from damaged tissue and injured endothelium. The nonstimulated platelet, which is discoid in shape, undergoes a conformational change when activated. The activated platelet is spherical, extrudes pseudopodia, and expresses an increased number of activated surface receptors that can be measured to quantitate the degree of platelet reactivity. The intensity of this platelet activation occurs in proportion to the quantity and nature of the platelet stimulus and increases in a graded fashion with increasing concentrations of agonists.

Once activated, these cells avidly adhere to basement membrane cells, leukocytes, other platelets, and nonbiological surfaces such as the cardiopulmonary bypass circuit. The platelet receptor which mediates this adhesion is the glycoprotein Ib (GPIb) receptor. GPIb receptor activation allows for binding of von Willebrand factor (vWF), collagen, and other circulating and endothelial ligands (13,14). Once activated, the platelets undergo a phase change that allows them to spread over the surface of injury, become more spiculated, less spherical, and to release the contents of their granules. This is an ATP-dependent process that requires the internal release of calcium and actin and myosin contraction. As granule contents are released, other platelets are attracted, and the formation of a platelet plug occurs. The platelet plug is of critical importance to stopping the oozing of surgical wound edges. Platelet plug formation is the body's initial step toward controlling microvascular (less than 50 μm vessel diameter) hemorrhage. However, the platelet-to-platelet interaction does not form a stable shear-resistant clot. It will hold together for only about 10 minutes and will certainly break down quicker if flow patterns or blood pressure disrupt its site of adherence.

Platelets are of crucial importance to the normal functioning of coagulation. Platelet morphology and biochemistry

are discussed in more detail in Chapter XX. In the current chapter, the interaction of platelets with the rest of the coagulation proteins and cofactors will be discussed. The platelet initiation phase and coagulation cascades may seem like separate processes, but they are completely interdependent. The glycoproteins on the platelet surface are the sites upon which the coagulation cascade proteases mediate their reactions (2,13,15–18). The GPIb receptor is the site for vWF binding. It is also the site for factor XIa to bind and then trigger factor IXa, leading to the macromolecular complex of factors X, VIII, calcium, and platelet factor 3 (the tenase complex) (2). Immediately adjacent to the GPIb binding site is the glycoprotein IIb/IIIa (GPIIb/IIIa) binding site. GPIIb/IIIa is the binding site for fibrinogen/fibrin (19). There may be 50,000 or greater GPIIb/IIIa binding sites per platelet membrane when they are fully expressed (20,21). Each fibrinogen molecule can bind up to six GPIIb/IIIa binding sites. Therefore, the possibilities for molecular interaction and cross-linking seem nearly infinite when one realizes that fibrin-to-fibrin interactions are possible between multiple molecules.

Coagulation monitoring in the laboratory is limited by the paucity of tests designed to measure the platelet-to-fibrin interactions. The prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT) all examine the proteins as they are artificially stimulated in plasma. Therefore, these tests, although useful, provide little or no information regarding the way in which in vivo human coagulation proceeds.

Once the coagulation cascade has been activated, the platelet plug may become stabilized with fibrin deposition and attachment of fibrin to platelets, thereby creating a more resilient and maturing clot. However, the clot still has to undergo considerable maturation. Fibrin is cross-linked and further stabilized by factor XIII. Factor XIII also incorporates alpha-2 antiplasmin, thereby building into the matrix a protection from fibrinolysis (22,23). The platelets continue to undergo cytoskeletal contraction, and this in conjunction with the covalent cross-linking creates clot retraction. The acceleration phase of coagulation would continue unimpeded if it was not for the control phase of the wave of coagulation. Indeed, in some disease states such as vasculitis, sepsis, and endothelial intoxication from drug overdose, there is no ability to control coagulation and diffuse intravascular coagulation does occur.

As platelets are stimulated and they interact with the protein cascade, certain regulatory proteins are released that downregulate the coagulation reactions. As thrombin is formed and as platelets are activated, thrombomodulin (a natural anticoagulant) is released. This in turn activates the protein C and S axis that leads to decreased production of thrombin (24–27). Endothelial cells respond to thrombin by releasing tissue plasminogen activator, which in turn catalyzes the production of plasmin from its inactive zymogen plasminogen (26). Plasmin not only causes the breakdown of fibrinogen and fibrin but also has profound effects on the glycoprotein binding sites of platelets. As mentioned earlier, it is the GPIb receptor that is responsible for adhesion to the endothelial basement membrane, and it is the GPIIb/IIIa receptor that mediates fibrinogen-platelet bonding. Plasmin, at normothermia, destroys or disrupts GPIIb/IIIa binding sites (9,27,28). Plasmin also cleaves vWF and attacks the GPIb binding site (18,28,29). The end result is platelet dysfunction, which can manifest as a weak and labile platelet plug and hence an unstable clot. Other regulatory mechanisms exist in local normally functioning endothelial cells which will help to limit the spread of coagulation by releasing their normal surface anticoagulants.

After the predominance of activity within the developing clot has shifted from acceleration to control, eventually a much longer and slower phase will prevail. This is the lysis phase, and plasminogen slowly breaks the bonds of fibrin. Plasmin's initial effects are to cleave fibrinogen, releasing fibrinopeptide A and B. Both of these are prothrombotic and create feedbacks to activation of thrombin. The fibrin molecule will break down eventually to D-dimer, which itself is an anticoagulant, inhibiting some of the serine proteases of the intrinsic cascade. Depending on the blood flow, level of cross-linking by factor XIII, and the amount of alpha-1 antitrypsin incorporated, the amount of time for clot lysis may be hours to several days in normal healthy organisms.

THE COAGULATION PROFILE

No amount of coagulation monitoring will replace a good history and physical; however, history is by far the more important. A few moments asking probing questions couched from the point of an informed examiner will be so much more cost-effective than widely applied screening tests. Patients with a rare congenital coagulopathy most often will not be discovered at the time of surgery but will be known from prior experiences. Hemophilia, vonWillebrand's disease, and Christmas disease patients generally have had a long family history and an adequate workup by a hematologist. However, if one asks about bleeding with dental hygiene, abnormal menses, and bleeding with otherwise minor or incidental trauma, you may uncover a patient who has not had a workup. For infants and small children, it is worthwhile to ask the parents about family history; however, remember that many of these are recessive and therefore it is entirely possible that both parents have not had a bleeding history or are from point mutations in one chromosome and

have a recessive characteristic from the other parent. The reader is referred to Chapter 6 regarding the congenital coagulopathies. Many of these patients may have recent administrations of factor replacement (factors VIII and IX) or D-8-amino arginine vasopressin (DDAVP) therapy. Repeat factor levels should be assessed in advance of a major surgery to ensure that appropriate levels are still circulating.

Platelet function or early platelet lysis abnormalities can occur because of idiopathic thrombocytopenia and drug-induced or associated poorly understood viral syndromes. Often these will present with spontaneous subcutaneous petechiae. Rarely do such abnormalities create as their first manifestation a bleeding into a hollow viscus, brain, or joint. However, if a patient does complain of one or more of these undiagnosed problems, it is certainly worth delaying elective surgery and asking for the hematologist to assist in the diagnosis.

Hemostasis testing varies among institutions. Most often the coagulation profile consists of a platelet count, fibrinogen concentration, PT, aPTT, and TT. Sometimes a fibrin degradation products level and a euglobulin lysis time may be included. Using a coagulation profile for patients to screen for abnormal bleeding is simply not cost-effective. Each test costs somewhere between $5 and $20. The entire coagulation profile may be $25 to $75 or higher, depending on the institution and the exact tests included. There are no data to suggest that abnormal test results portend a large risk of bleeding, and there are certainly no data to suggest that it is cost-effective to screen the population who have a negative history (more than 20 million operations per year).

Platelet count can be reliably obtained today using automated cell counters. This test had previously been performed manually by a technician by counting platelets in a special slide well that had a defined volume and a grid pattern to allow identification of known size areas. The manual technique, as one might expect, has a considerable amount of inter-technician variability and is therefore simply not reliable. The present-day automated counters use laser technology to size the various cells or particles, and some have the ability to classify intracellular organelles such that they define a cell type not only by size but also by morphology. Automated flow also is used in the newest models to identify cell lines by the type of cell adhesion molecules.

Circulating platelets are anucleate discoid-shaped cells that are formed from megakaryocytes. A normal component of platelets includes a normal count (150,000 per μL to 450,000 per μL) and normal function. It is important to appreciate the many different roles that platelets have in maintaining circulation and hemostasis. Platelets form the primary phase of hemostasis, the platelet plug. This initial adhesion of platelets to the injured endothelium is responsible for the physical healing of the wound, and the biochemical signaling that occurs when other cells and coagulation factors are summoned to the site of injury. The platelet surface phospholipids is a critical surface upon which the coagulation cascade proteases become activated and form a fibrin clot. On physical examination, the absence of normal platelet number or function can be detected by the presence of petechiae. Conversely, an excessive number of platelets or excessively activated platelets will predispose to arterial occlusive disease. Patient history and family history are the most important factors in assessing platelet-related disorders.

Routine screening for platelet abnormalities is not recommended in the absence of any of the signs or symptoms noted above. When the need for platelet testing has been established, a platelet count is obtained. Thrombocytopenia exists, by definition, if the platelet count drops below 150,000 per μL.

A minimum platelet count of 50,000 per μL to 100,000 per μL is recommended prior to elective surgery. Spontaneous bleeding can occur with platelet counts less than 30,000 per μL. However, in the cancer chemotherapy patient spontaneous bleeding may not be seen until the platelet count is well below 5,000 per μL. Therefore, it is possible that bleeding may not be an issue until such low levels are reached if all other factors are normal. Most anesthesiologists and surgeons would prefer not to be at the absolute limit of normal coagulation, and the standard recommendations in texts are a minimum of 20,000 to 50,000 per μL for elective surgery and 100,000 per μL for CPB. Of course, if the platelet function is abnormal, a platelet count of even 150,000 per μL or greater may be insufficient to ensure normal coagulation.

Further testing such as the bleeding time and other aggregation studies will be described as they relate to individual disease states.

Thrombocythemia is defined at levels of platelet concentration that exceed 450,000 per mL. It is unclear at what level there is an increased risk of thrombosis or embolic phenomenon. Perhaps the interaction of the platelets with endothelial cells and fibrinogen is more important than simply the number expressed per microliter. Hypercoagulability has been shown recently with certain genetic alleles of platelet surface GPIIb/IIIa ligands (21,30,31). This may result in an increased risk of early myocardial infarction, (32) or other thrombotic events, but the risks in the perioperative period have not been confirmed.

There is no level of blood loss or euvolemic hemodilution at which a prophylactic platelet transfusion should be given. As blood is lost and intravenous crystalloid or colloid is administered, there is a slow and often predictable level of hemodilution that does occur. Several studies have examined the predicted level of platelet count (32,33). There

have been computed slopes for platelet count reduction as hemodilution occurs. However, the actual measured platelet count never fits that expected by hemodilution alone. Rather, the actual count always exceeds that level as platelets are released from marrow, splenic, and hepatic stores in response to stress. Therefore, there is no reason to transfuse platelets for any given amount of blood lost. If the platelet count has been normal or is assumed to be before surgery or before a traumatic event, then one can expect at least one blood volume to be lost before the platelet count reaches levels that may be critical. In studies of patients suffering massive trauma, most patients who had undergone a blood volume blood loss still had a platelet count in excess of 100,000 per μL (32,33). Platelet counts can now be performed so rapidly that there is little if ever a reason to transfuse patients on clinical indications for suspected low platelet counts. Platelet function abnormalities may be a different problem and are dealt with later in this chapter.

The measures of protein cascade function are generally broken down into three major tests: aPTT, PT, and TT. These three tests respectively examine the intrinsic and extrinsic cascades and the final common pathway (i.e., fibrinogen to fibrin). These tests should be considered as screening tests for overall protein function. Initially, these tests were created to detect congenital coagulation defects or to follow problems of hepatic failure. They were created at the time when the coagulation cascades were being described and characterized. They were not initially intended to find any particular risk for coagulopathic bleeding after surgery.

The classic teaching of the coagulation mechanism has focused on the trisection of the protein cascades. Perhaps it is easier to learn if one has a schematic that nicely compartmentalizes certain protein reactions. These tests have a low negative predictive value in cardiac surgery. If they are normal, this is not a guarantee that the patient will not bleed. Similarly, if they are abnormal, this does not mean that they should be treated before surgery.

These three screening tests of protein coagulation function do not mimic in vivo coagulation; however, they will detect congenital abnormalities and the effects of hepatic failure. Furthermore, the aPTT is useful for following the dosing of low or moderate dose heparin therapy and the PT is useful for following Coumadin or warfarin therapy. One should understand how each test is performed to get an appreciation for their limitations and clinical worth.

The aPTT is performed in an automated system that stimulates plasma with a contact activator. Most often this is either Kaolin (aluminum silicate) or celite-diatomaceous earth (sodium silicate). Other contact activators can be used as well. Aluminum silicate is an artificial product that has the potential for being standardized more readily than diatomaceous earth. Celite is isolated from clay deposits that are heavily laden with the microskeletons of diatoms (prehistoric protozoan-like creatures). Either one of these stimulating agents causes the initial activation of Hageman factor and leads to factor IXa and then factor Xa production. The assay does require the competency of the final common pathway as an automated fibrometer detects the earliest formation of fibrin strands. Therefore, the entire test looks only at the time to initial fibrin strand formation when isolated plasma is artificially stimulated for contact activation. Hypofibrinogenemia (<75 mg per dL), dysfibrinogenemia, or excesses of fibrin degradation products may prolong this test (predominately through D-dimer); D-dimer will inhibit the function of factor IX. The test is sensitive to heparin activity in low to moderate dosages because heparin is an antithrombin that blocks thrombin's action on fibrin and also has weak effects on certain serine proteases (most notably factor IXa). The aPTT has a reproducible sensitivity range up to about 100 to 129 seconds. Beyond that level, the data become much less reproducible, and if heparin has been administered such that the aPTT is prolonged beyond that range, then some other test must be used to follow it (the activated clotting time (ACT), or a titrated heparin concentration (Hepcon, Medtronic Inc.) (33).

What is a safe aPTT for patients to undergo surgery? Unfortunately, there is no easy answer to that question, because the circumstances are always different. Perhaps a level of 1.5 to 1.8 times normal should be considered an appropriate level above which the risk of bleeding may increase. However, a linear relationship has not been shown between the relative abnormality of the test (aPTT) and the amount of postoperative or intraoperative bleeding. Also, since heparin can be reversed with protamine administration, rapid restoration of the aPTT to baseline is easily accomplished if surgery is imminent. There are also no data to suggest a safe threshold of aPTT above which a spinal or epidural block should not be placed. This is probably one question that will not be answered using randomized controlled trials since clinicians are not willing to take the risk of a neurological injury of potentially catastrophic proportion in the face of abnormal coagulation testing.

The PT like the aPTT is performed by automated equipment using isolated plasma. It is interesting that this test examines the extrinsic coagulation cascade as bovine thromboplastin or tissue factor is used as an activator for the factor VII activation. This test, like the aPTT, proceeds from the time of active stimulation until the first strands of fibrin are formed. It is also a timed test. The PT is a screening test for the relative activity of the vitamin K dependent hepatically produced coagulation proteins (factors II, V, VII, and X). Therefore, it is useful in following drugs that directly influence these factors production and the synthetic capabilities of the liver. Indeed, in end-stage liver

failure and in hepatic transplantation, it can be used to follow organ function. The PT is an interesting example of how these tests, although useful, do not mimic normal human coagulation. A significant number of crossovers in activation occur in vivo between the intrinsic and extrinsic cascade. For example, factor VII can activate factor IX and in turn lead to activation of factor X. However, this activation must occur on the surface of activated platelets at the GPIB binding site. The PT test has no platelets and hence no glycoprotein binding sites allow this cross-activation. What does the PT mean then in the context of the intact human that has functional platelet surfaces? That question is hard to answer because, like the aPTT, there are no data to correlate any given PT with a certain risk of hemorrhage. But once again, if the PT is 1.5 to 2 times normal, then the risk of hemorrhage may indeed be elevated (34).

The International Normalized Ratio (INR) is a method of comparing the patient's activity with a known standard run each day with the batch of activator to be used for that run of samples. This may also limit the variability from laboratory to laboratory, and if one speaks of INR, then it is easier to compare. Because the activator for the PT is derived from a biological source and therefore each batch may have a different activity profile, it is necessary to run a standard for comparison (35). An INR of 1.5 at one institution should be the same as an INR of 1.5 at another, although the actual PT numbers may differ considerably. Therefore, when we consider the risk of hemorrhage, an INR of 1.5 to 2 could represent an increased risk for hemorrhage.

The aPTT is used to follow low to moderate dose heparin, usually given in the intensive care unit and routine nursing floors either for deep vein thrombosis (DVT), myocardial ischemia, or other embolic prophylaxis or treatment. Therapeutic ranges for the aPTT and heparin dosing differ again from center to center, but usually raising it to 1.5 to 2 times normal seems appropriate. The heparin is cleared by combined hepatic and renal clearance and should have a $t_{1/2}$ of 90 minutes to 4 hours. One can always reverse residual heparin with protamine, but simply performing an ACT alone and finding it normal will not mean that all amounts of trace heparin are reversed. The ACT is not sensitive enough a test to detect low levels of heparin effect. In medical practice, if the heparin is turned off 2 to 4 hours before surgery, usually the aPTT will return to normal. Either a repeat aPTT or a TT can be used to prove that trace heparin has been neutralized. A test of whole blood clot strength, the thromboelastograph (TEG), may be the most sensitive to trace heparin, but this is not available at many centers.

Another potential prolongation of the aPTT exists with lupus anticoagulant. This is really a misnomer, because there is not truly any effect on coagulation function. Rather, an immunoglobulin is present in the serum that binds to the activator in the aPTT causing the aPTT to be elevated and unreliable as an indicator of abnormal intrinsic cascade function. Inhibitors of factors VIII and IX, and the lupus anticoagulants are the most common inhibitors encountered. The lupus anticoagulants are antiphospholipid antibodies that react with the phospholipid surfaces required for coagulation, thus prolonging clotting time in vitro. In patients who do not have systemic lupus, this syndrome is referred to as primary antiphospholipid syndrome. Testing for this immunoglobulin has been performed using the aPTT or a dilute viper venom time. The latter consists of activation of factor X by venom and measurement of the clotting time, which will be prolonged if an inhibitor is present. Immunologic assays for anticardiolipin antibodies are available. Patient serum is incubated with solid-phase cardiolipin and bound immunoglobulin is measured. Lupus anticoagulant will also affect the ACT and make it unreliable for monitoring heparinization during cardiopulmonary bypass. Lupus anticoagulant can be found as an isolated finding but most often is associated with immunoglobulins produced due to a malignancy. Congenital coagulopathies of the intrinsic cascade may be discovered and followed with the aPTT such as Factor XI deficiency. This is seen in some Eastern European Jewish populations. In one study among this population, 10 cases were found in 1,148 presurgical patients screened. It is possible for bleeding to result after surgery if this condition is undiagnosed. However, in other populations, the disease is so rare that it may not be cost-effective to screen for it with the aPTT. The aPTT can identify von Willebrand's disease, classic hemophilia or hemophilia A (decreased amount of factor VIII), and Christmas disease (factor IX deficiency). The congenital deficiencies are marked by absent levels of factors or abnormal function of factors. Since it takes only 20% to 30% of these proteins to contribute to a normal aPTT, an abnormal aPTT would be an indication of severe deficiency. Thus, aPTT is an effective screen for these congenital deficiencies, Restoration of coagulation before major surgery in the face of these congenital abnormalities makes sense using the aPTT as a guide, but more often, assays for the levels of the particular deficient protein will be followed.

The TT tests the final common pathway and is performed in some ways similarly to the aPTT. That is, the plasma is separated from the red cells, platelets, and white cells using centrifugation and then the plasma is artificially stimulated. Once activated, the time until initial fibrin formation is timed using a fibrometer (now completely automated). The activator is usually bovine thrombin, and this directly activates fibrinogen to polymerize into fibrin. Clearly, if heparin and antithrombin III complexes are present, then the TT will be prolonged because the thrombin is bound to these complexes. Also, if dysfibrinogenemia exists such that the fibrinogen is congenitally dysfunctional, a

prolongation will exist also. If the fibrinogen concentration is extremely low, the TT will also be prolonged (probably less than 25 to 30 mg per dL). At this low range of fibrinogen, diffuse and potentially severe bleeding during surgery is possible as well. If heparin is present and the amount of final common pathway function needs to be assessed, then a reptilase time can be performed. This test uses a viper serum to activate the fibrinogen to fibrin reaction, and unlike thrombin, that serum protein is not able to attach to heparin-ATIII complexes.

The fibrinogen concentration can be assayed by either a dilutional technique, using thrombin as an activator in different dilutions of plasma or by immunoassay. Fibrinogen concentrations greater than 100 mg per dL are sufficient to have normal clot function, if other functions of the clotting system are normal. Usually, in dilutional states, if there is dilution of fibrinogen concentration to these concentrations, then dilution of other factors such as factor V and VIII and platelets will occur. If hypofibrinogenemia exists from hepatic failure or from drug effects, then again multiple other problems probably exist and the fibrinogen level will not be the only risk for bleeding. Following fibrinogen as an indicator of the amount of hemodilution is not necessarily accurate, because fibrinogen is released from hepatic stores in response to stress. This release is less pronounced than is seen with platelet activation. If one is transfusing packed red cells, one should remember that these carry small amounts of plasma and therefore fibrinogen will decrease. Cell salvaged blood (from washed processing systems) carries no plasma at all and that from nonwashed systems may have variable amounts of fibrinogen and fibrin degradation products present, because this blood usually has undergone some element of coagulation and fibrinolysis before collection. Modified whole blood has had cryoprecipitate removed and therefore its fibrinogen concentration is about one-half normal.

Many other tests of individual procoagulant protein precursors can be assayed for particular concentrations. Some are performed using dilutions of plasma with the activators used in the PT and aPTT and yet others require chromogenic, ELISA, and radioimmunoassay tests. It is beyond the scope of this chapter and not necessary for the surgical/anesthesia practitioner to know how each of these assays is performed. Usually, if a particular factor level is low, a hematology consultation should be involved to follow the patient. Particular protein factor levels can be assayed, but these tests are often expensive and cannot be quickly and routinely run. Therefore, they are not of great use during the dynamic events of surgery but may be useful in the preoperative assessment of a congenital or iatrogenic abnormalities. Coagulation abnormalities can be caused by deficiencies of normal coagulation proteins, dysfunctional protein activity, or antibodies to these proteins. Rarely, an immunoglobulin cross-reacts with a protein and causes an isolated coagulopathy (i.e., IgG to factor V or VII). Again, an expert hematologist will be required to guide diagnosis and therapy for such patients before and during surgery, but the suspicion of such a diagnosis may begin with a history of bleeding or an abnormal aPTT or PT. In yet another study examining 2,000 patients screened preoperatively with the aPTT and PT, only 0.5% of tests had an abnormality not expected by clinical history (36). Other studies have shown that the most common cause of abnormal studies when the history is negative is laboratory error (37).

All of the above-mentioned tests of coagulation have focused on the protein cascade in isolation from other elements of the blood. As stated, a great deal of useful information can be gleaned from these tests, but they also have considerable limitations. Whole blood point of care testing has now become available for the aPTT and PT (1). Using a capillary tube system that draws blood forward through a convoluted tubing system by capillary action, these systems measure the speed of advancement of a small drop of blood through the capillary tube system. When a drop of whole blood is placed on the disposable cartridge for one of these tests, the blood first mixes with a reagent before moving forward into the capillary tubes. The time until the leading edge of the advancing blood column stops is noted and using an algorithm to correct that time for a known compared standard, the aPTT or PT is reported. In other words, the whole blood aPTT or PT in time until the advancing column stops is not exactly the same amount of time as that for a laboratory plasma aPTT or PT. That is probably due to the fact that when whole blood is present and activated, the platelets become activated and release a number of compounds that amplify the coagulation reactions. The accuracy of these point of care systems has been compared with laboratory gold standards and the PT has good correlation coefficients, whereas the aPTT seems to have more variability (38). They are, however, useful even with these variations, and one cannot know which should be considered the most appropriate because blood coagulation in vivo occurs with all the elements interacting.

As noted previously in this chapter, the individual protein coagulation tests in isolation are not predictive of abnormal bleeding at surgery; certainly not until they reach levels of 1.5 to 2 times normal. This makes sense, as the human body has a wide range of redundancies, and an isolated abnormality in one test may not have clinical relevance. However, an approach looking at prediction of bleeding using an algorithm for these tests has been proposed and tested in relation to postcardiopulmonary bypass bleeding (Fig. 26.2) (1). By using aPTT, PT, and fibrinogen concentration, a branching algorithm for treatment of abnormalities has been tested. Using this algorithm, the

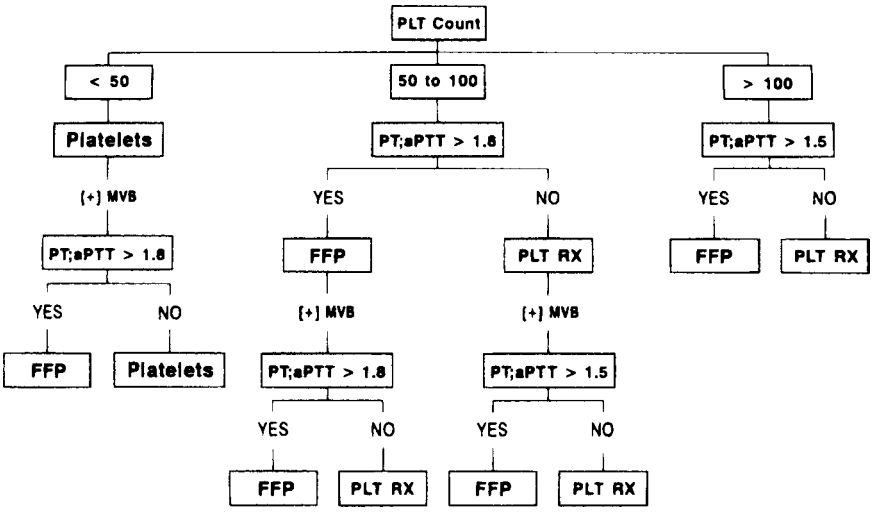


Figure 26.2 An algorithm for treating coagulopathies based on PT, aPTT, and platelet count. Note that this system attempts to discern platelet dysfunction by a process of elimination. (Reprinted by permission from Despotis GJ, Santoro SA, Spitznagel E, et al. Prospective evaluation and clinical utility of on-site monitoring of coagulation in patients undergoing cardiac operations. *J Thorac Cardiovasc Surg.* 1994;107:271.)

use of blood products was decreased in one trial. However, because the utilization of any rational approach to transfusion in cardiopulmonary bypass patients would be better than clinical judgment, it is hard to say at this time if this algorithm is the best way to approach all patients, or if any algorithm is beneficial. Essentially, the algorithm uses the protein coagulation tests, along with platelet number, to isolate platelet function abnormalities by process of elimination.

Another test of whole blood clot function looking at protein function is the ACT (39). This test uses either celite or kaolin to activate the intrinsic cascade. The concentration of activator is so high that it overcomes low and moderate dose heparin and yields a dose-dependent relationship to higher dose heparin. For cardiopulmonary bypass at the dosages of heparin used, the aPTT is prolonged beyond the range of its usable readings; therefore, the ACT is used for gauging heparin administration and dosing during cardiopulmonary bypass. The ACT was originally devised by Bull et al. (40) as a modification of a LEE-White whole blood clotting time. Essentially, whole blood is placed either in a glass test tube (either kaolin or celite) with premeasured activator or into a plastic well also containing activator (kaolin). If the test tube system is used, the tube rotates with a magnetic indicator-stirring the whole blood until the first gel formation occurs and the magnet is caught in the gel, triggering a detector that the clot has formed. If the well system is used, a plunger is lifted once every second and allowed to drop by gravity back through the whole blood. When the speed of descent of the plunger is slowed, due to initial gel formation, then the system is triggered and the time in seconds reported. The ACT produces a straight-line relationship between heparin administered and prolongation of the ACT, in seconds as long as certain criteria are met. These include normal AT-III concentrations, normal factor XII activity, normothermia, platelet number greater than 50,000 per mL, reasonable platelet function, and fibrinogen concentration greater than 100 mg per dL (41). These qualifiers do not always exist in the postbypass situation, particularly the presence of reasonable platelet function, platelet number, and fibrinogen concentration. The ACT warms the cuvettes to 37°C, but with cold blood from hypothermic patients or insufficient time for the device to warm the test tube before introduction of the blood sample, low temperature can significantly prolong the ACT. Therefore, there are other etiologies for a prolonged ACT in addition to the presence of heparin. At our institution, a dose–response curve is handdrawn for each patient before cardiopulmonary bypass (Fig. 26.3). A sample of blood is taken at baseline before heparin is given. After heparin administration, another ACT is run. A straight-line (two-point) dose–response curve is drawn. If the ACT does not reach the institutional acceptable level for bypass (ACT of 450 seconds), then the dose–response curve may be useful in judging how much additional heparin to administer. Also, the dose–response curve can be used during cardiopulmonary bypass to judge how much extra heparin is needed to maintain the ACT greater than 450 seconds.

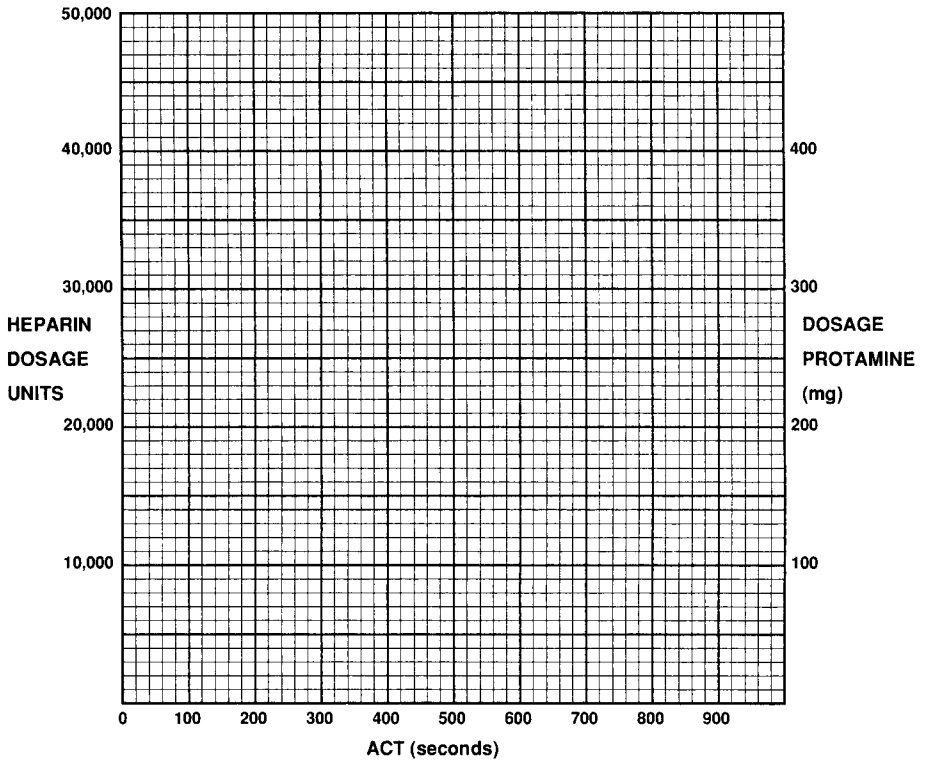
There is nothing magical about 450 seconds. The number derives from a paucity of scientific data and it is highly institutionally dependent. The heparin–ACT dose–response curve may have a different slope before, during, and after cardiopulmonary bypass, due to hemodilution, hypothermia, and other factors. However, it is impossible to continuously create new individual dose–response curves. The ACT after cardiopulmonary bypass should return to normal or actually below the number obtained for baseline if protamine is

PRE-BYPASS DATA						
PT	PTT	TT	Fib	Plat	Hgb/Hct	OTHER

TEG				
R	K	α	MA	A_{60}

MEDICATIONS

ACT HEPARIN-PROTAMINE ACTIVITY



TIME:

$ACT_{baseline}$ ____ ____

$ACT_{postheparin}$ ____ ____

$ACT\ CPB_1$ ____ ____

$ACT\ CPB_2$ ____ ____

$ACT\ CPB_3$ ____ ____

$ACT\ CPB_4$ ____ ____

$ACT\ CPB_5$ ____ ____

HEPARIN INITIAL _____

TOTAL HEPARIN _____

PROTAMINE _____

POST CPB												
ACT	TEG											
	R	K	α	MA	A_{60}							

POST OPERATIVE												
ACT	TEG											
	R	K	α	MA	A_{60}	PT	PTT	Fib	FSP	TT	Plat	Hgb

PT.NO.

NAME

D.O.B.

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CARDIOPULMONARY BYPASS COAGULATION REPORT

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Figure 26.3 The heparin dose–response curve used as a modification of a standard "Bull" wave. Of note is that the protamine dose can be calculated in a 1:1 dosing schema from the last activated clotting time before weaning from cardiopulmonary bypass.

administered. If the ACT is still prolonged above baseline, then an excess of protamine may have been administered, heparin may still be active, or an abnormality of the coagulation cascade exists. Again, at our institution, the ACT dose–response curve drawn before cardiopulmonary bypass is used to calculate a protamine dosage (Fig. 26.3). The last ACT before separation from cardiopulmonary bypass is translated into a protamine dose based on an arbitrary titration of 1:1 heparin activity to protamine administration. The in vitro work with protamine has shown that it is capable of reversing heparin at ratios as low as 0.33 mg protamine per heparin dosage (42). If the ACT is mildly prolonged and protamine is given in an attempt to neutralize any remaining heparin, the ACT should shorten. If it stays the same or lengthens, then thrombin inhibition by protamine is probably present and further administration of protamine will only cause more anticoagulation.

The ACT is not a predictor of abnormal bleeding. Clearly, moderate prolongations of the ACT after cardiopulmonary bypass might suggest an increased risk of bleeding, but a normal ACT is meaningless because of the low sensitivity of the test. The ACT is an insensitive test for trace amounts of heparin, and some argue that trace or reheparinization can occur even with normal ACT levels (43). How much these events contribute to chest tube bleeding is unclear. Unfortunately, the aPTT is mildly prolonged by cardiopulmonary bypass alone, and it may well be that the heparin–protamine complex partially inhibits the activators or that the platelet inhibition found after cardiopulmonary bypass decreases the platelet amplification of the intrinsic coagulation cascade. ACT levels of 1.5 to 1.8 times normal may well be physiologic after cardiopulmonary bypass and do not connote any increased risk of hemorrhage, The TT and TEG may be followed for trace heparin levels.

The ACT gives a bioassay of heparin activity in whole blood. However, one can get chromogenic heparin levels (the gold standard) if circulating heparin concentration is needed. These are expensive, not done at every institution, time-consuming, and are therefore not of practical value for routine surgery (cardiopulmonary bypass). They should be reserved for research. However, a POC heparin assay is available (Hepcon, Medtronic Inc.). This automated system uses wells with premeasured activator (kaolin) heated to 37°C, much like the ACT test. The heparin concentration assay has different aliquots of protamine in the wells. When blood is put into these wells, the well that clots first will have protamine in close approximation to the amount of circulating heparin concentration. Several different cartridges are available with ranges of possible circulating heparin concentration. There is some debate as to whether it is more favorable to have patients managed for cardiopulmonary bypass using a target heparin level in the blood or whether it is better to use the ACT. Those who support ACT management argue that ACT is a functional test of heparin activity, whereas the target heparin level is a relative clotting time that compares one well to another. It does not strictly examine the functionality of heparin and AT-III complexes.

Another set of cartridges in this device is the heparin dose–response assay. Each well has a known amount of heparin in it, ranging from zero to 1.5 U per ml to 2.5 U per ml. Using the clotting times, the machine can construct a heparin dose–response curve and will tell the practitioner how much heparin to administer to achieve a given ACT.

Comparisons of Hepcon-managed versus ACT-managed coagulation during cardiopulmonary bypass have shown some improvement with the Hepcon system for perioperative bleeding (43). However, these studies compared the Hepcon system to ACT-based management for heparin initiation and maintenance (44). But protamine calculations in the ACT-based group were administered by a calculated 1.3 times the total dose of heparin, as compared with a protamine dose–response curve, generated by the Hepcon system. These results may well reflect a relative overdose of protamine compared with dose–response curve managed therapy (42). In one study at our institution where the Hepcon system was used for research and therapy was based on the maintenance of a constant level of heparin circulating at 3.4 mg per mL, more heparin and therefore more protamine were given than would have been given otherwise. The Hepcon automated dosing system is effective if the team managing the patients is interested in maintaining stable heparin levels. However, this system is considerably more costly than routine ACT management. The inserts for testing heparin levels are more than $10.00, and the cost for an entire case to manage therapy may be in excess of $100.00.

Platelet counts are readily available using automated devices with laser technology. These Coulter counters separate out populations of particles based on size. Computer programming of the systems means that certain sized particles will be deemed platelets, others white cells, and still others erythrocytes. The newest technology not only sorts the cell types by size but also by intracellular organelles and in some flow-cytometry. It appears that the newest cell counters can distinguish between perfluorocarbon emulsions (no intracellular inclusions) and platelets.

We can count platelets, and a good clinical laboratory should be able to give rapid turnaround from sample collection to data, reporting such that the dynamic situation in the operating room can use these data. However, the real time ability to follow platelet function has always been more of a challenge. Platelet aggregometry can be performed to evaluate certain platelet function abnormalities. These tests use the patient's platelet-rich plasma to

which a certain known concentration of the patient's own plasma has been added back to control platelet count. An aggregometer is a warmed chamber through which a light is shined, and detected on the other side of the sample. The turbidity of the system and hence the density of the platelets will determine light transmission. When a stimulating chemical is added to the system, the platelets will begin to clump and precipitate, decreasing the turbidity of the sample. One can perform platelet aggregometry without any in vitro stimulus. Recently, it has been shown that if patients have an abnormally fast spontaneous platelet aggregometry, then their risk for myocardial infarction and unstable angina may be increased (45). That means that spontaneous platelet aggregometry may be a test for increased platelet activity or stickiness. Many other compounds can be added as stimuli for platelet aggregometry, including ADP, collagen, epinephrine, serotonin, ristocetin, platelet activating factor, fibrinogen, and thromboxane. Although abnormalities may be demonstrated in one or more of these artificially stimulated platelet aggregation tests, it is difficult to infer from any one test a certain increased risk of bleeding. Because these require precise measurement of platelet concentration and resuspension of platelets in plasma, the amount of technician time required to perform these tests prohibits them from being of utility during surgery.

The bleeding time is a crude test of platelet plug formation that has been of historical and clinical interest. A small controlled cut is made by a spring-loaded template either on the inner surface of the forearm (Ivy) or on the pinna of the ear (Duke). If the arm is used, a tourniquet is inflated to 40 mm Hg above the site of the template scratch and maintained that way until the test is completed. Filter paper is used to blot (not wipe) the wound every 30 seconds until the bleeding stops. It is considered stopped when the filter paper no longer absorbs blood. As such, the test would appear to examine the speed of formation of the initial platelet plug, but a wide range of problems exist with this test. In healthy young volunteers, a number of studies demonstrate that if the bleeding time was normal before the administration of a particular medication known to influence platelets (nonsteroidal anti-inflammatory drugs) and another bleeding time is then performed, the second one will be prolonged. From these data, practitioners have assumed that they will then be able to detect platelet dysfunction in other groups of patients. The fallacy behind that argument is that if one tries to apply the bleeding time to patient populations that might be at risk for bleeding from platelet dysfunction, other etiologies of a prolonged bleeding time exist.

Temperature of the skin, presence of extra cellular fluid (edema), skin blood flow, the use of catecholamine or vasodilator drips, and muscle tone, may all affect the bleeding time. In surgical patients, skin temperature and blood flow undergo wide fluctuations. One can see that these other variables may be present to create either spuriously prolonged or shortened bleeding times. Several recent reviews of the literature on the bleeding time have been written, and they have concluded that the bleeding time has no use in predicting a risk for abnormal hemorrhage during or after surgery (46). Furthermore, some institutions will perform a bleeding time before the placement of certain regional blocks or in pre-eclampsia or eclampsia. The physiology of the platelet plug as an isolated event in hemostasis has little to no relationship to the risk of bleeding in the in vivo physiologic situation of surgery or regional anesthesia. There are no data at all in the literature supporting the use of a bleeding time in deciding whether a patient can or cannot receive an epidural. The bleeding time in cardiopulmonary bypass patients, a group with universal platelet dysfunction, has had no predictive value in most studies. Only if the bleeding time is massively prolonged does the specificity of the test become reasonable. The logistical problems alone make performing the bleeding time prohibitive for most surgeries.

Whole blood clot testing for viscoelastic properties has gained popularity in the perioperative period (47). Two tests presently exist to test such properties. The properties of clot strength change over time, and viscosity changes may be quite important in predicting hemorrhage. In the end analysis, clot is merely the interaction of platelet surfaces with fibrin. Of course, fibrin cross-linking the presence of other cell types such as white cells and erythrocytes enmeshed within the clot may have importance. The screening tests of protein clot function are all in vitro tests that examine only one small part of the coagulation process. As stated earlier, the protein cascades do not exist separated from the platelet surfaces in vivo. Therefore, although we may be able to demonstrate abnormalities in the aPTT or PT, when these prolongations are mild to moderate, it is hard to find any increased risk of bleeding. Fibrinogen has six binding sites for GPIIb/IIIa. The interaction of fibrin with these surface receptors is vital to the strength of a clot. The interactions of platelet to platelet stimulation (formation of the platelet plug) in an acceleration phase of coagulation and with the protein cascades are important. These events lead to the rapidity with which clot strength grows.

The TEG is a test of whole blood clot strength and was first invented in 1947 by a German hematologist (55). Its mechanism uses a warmed cup or crucible previously made of stainless steel but now made of disposable plastic. Suspended inside the cup is a piston that does not touch the walls of the cup. The cup moves through an arc of 4.5° once every second, pauses for 1 second, and then moves back

through the arc in the opposite direction. There is no connection between the cup and the piston until whole blood is placed in the cup and coagulation begins. A small amount of blood is needed to perform this test (0.35 mL). In routine TEG, coagulation begins with spontaneous stimulation of the intrinsic cascade (48). The noninert surface of the original stainless steel cups and pistons provided a stimulus to coagulation. With the current disposables, an activator is needed because the onset to coagulation is quite variable, probably due to imperfections in the plastic. Celite, kaolin, or tissue factor have all been used to activate the TEG.

The TEG measures clot strength over time by maintaining the piston stable in an electromagnetic field. A paper tracing relates the amount of power necessary to maintain that as the rotational motion of the cup is transferred to the piston. This paper tracing has an amplitude at any given time and is displayed in Figure 26.4. Standard parameters can be measured from the TEG tracing (Fig. 26.5). Probably, most important is the maximum amplitude (MA) and that measurement is the paper representation of the

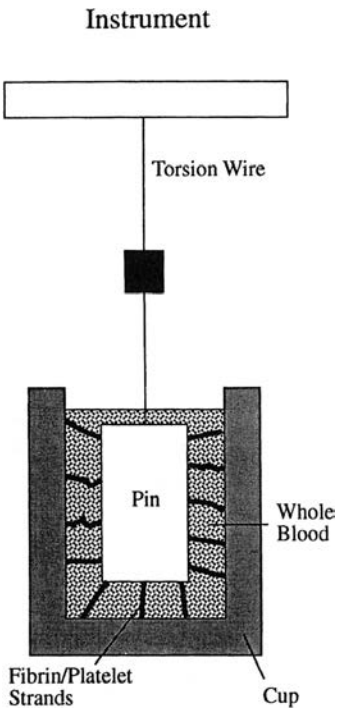


Figure 26.4 The TEG mechanism uses a cuvette warmed to 37°C that rotates through a 4.5° arc. Suspended inside that cuvette is a piston. Whole blood (0.35 mL) is placed into the cuvette and as coagulation progresses, platelet/ fibrin strands form between the cuvette and the piston. An electromagnetic field holds the piston steady and the paper trace then reflects the energy necessary to hold the piston stable. The TEG simply tests clot strength over time. (Reprinted by permission from Chandler W. The thromboelastograph and the thromboelastograph technique. *Semin Thromb Hemost.* 1995;21(suppl 4):1–6.)

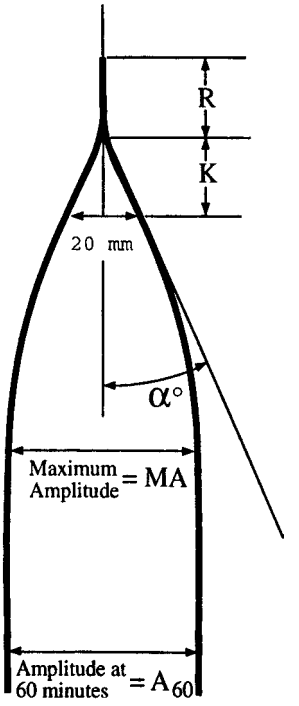


Figure 26.5 The TEG tracing has standard parameters that can be measured, including R value (onset of test until amplitude is 2 mm); K value, from the end of R until amplitude = 20 mm; a angle, a measure of the angle to the upslope of the TEG trace; A_{60}, the amplitude 60 minutes after the MA. (Reprinted by permission from Chandler WL. The thromboelastograph and the thromboelastograph technique. *Semin Thromb Hemost.* 1995;21(suppl 4):1–6.)

maximum clot strength. Clot strength is related to amplitude by the equation G = 5000 (A)/ 100 - A, where G is measured in dynes/cm^2 and A is the amplitude at any given time. The relationship of G to MA is curvilinear and logarithmic because the MA is measured on a scale of 0 to 100 mm, whereas G goes from 0 to ifinity (Fig. 26.6). Therefore, small or moderate changes in MA may translate into considerably larger changes in actual clot strength (G force). Most papers report the MA, but one wonders if it is not more appropriate to speak in terms of physical force.

The TEG examines whole blood coagulation from the time of initiation through acceleration, control, and eventual lysis. It can tell us essentially only four major things about coagulation: how fast the clot forms, the speed of clot growth, clot strength, and whether clot strength is maintained or breaks down early. These four facts about clot function are the crucial elements in whether a patient bleeds or not. If they are all normal, a significant coagulopathy cannot exist.

The physical strength of clot is dependent on the interaction of platelets and fibrin. Work has shown that platelets have about twice as much effect on the MA as

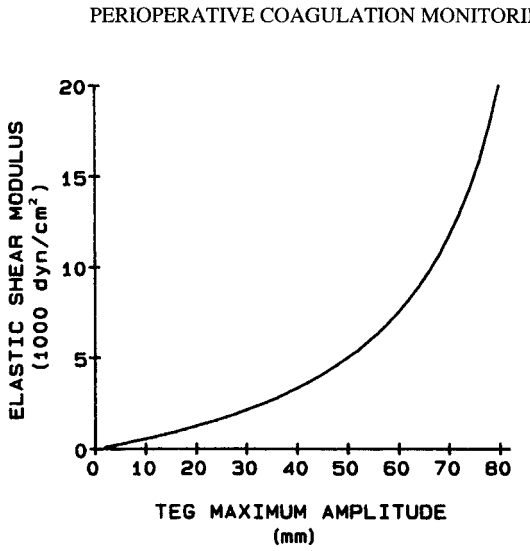


Figure 26.6 The maximum amplitude is related to clot strength (G) as a logarithmic function. The mean for the population is approximately 5000 dynes/cm^2 or 50-mm amplitude. Notice that if the amplitude decreases from 50 to 35 mm, a 30% reduction in MA, the force is decreased by 50% or more. (Reprinted by permission from Chandler WL. The thromboelastograph and the thromboelastograph technique. *Semin Thromb Hemost.* 1995;21:1–6.)

does the fibrinogen concentration alone (49). Recent work with glycoprotein-blocking agents have shown that the TEG MA relates closely to the dosage of blocking agent administered, whereas the TEG MA has little or no relationship to changes in ADP platelet aggregation (50). TEG with tissue factor acceleration speeds the appearance of MA and is accurate for monitoring the platelet inhibition by large concentrations of GPIIb-IIIa receptor blockers. Using this technique with platelet-rich plasma, the reduction of the MA has been used as an index of platelet inhibition by GPIIb–IIIa receptor blockers in the catheterization laboratory. Comparison with the baseline MA yields a relative measure of the degree of platelet inhibition. Thrombin receptor agonist peptide (TRAP)– induced aggregation correlates strongly with the TEG values measured in this fashion (50).

The TEG is relatively insensitive to the changes found with aspirin therapy (48). Aspirin blocks thromboxane production in platelets as they are generated. However, there are multiple pathways by which platelets are activated, and if one supposes that the blood sample in the TEG is activated by the intrinsic pathway, then thrombin will be the chief mechanism for platelet activation, not thromboxane.

The TEG was first used in surgery for the monitoring of coagulation in hepatic transplantation (51). On-site rapid coagulation assessment was necessary because the changes of coagulation during these long and complex cases were profound. TEG technology has also been applied to cardiopulmonary bypass patients, with many studies showing it to be the single best predictor of abnormal postoperative hemorrhage (52–56). One particular study examined the sensitivity and specificity of the TEG test as compared with other protein coagulation tests, platelet counts, and the bleeding time (57). The TEG had the best sensitivity and specificity of any coagulation test examined. The efficacy of the TEG for predicting surgical bleeding (a normal TEG) is greater than 90%.

The use of TEG in guiding coagulation therapy or in detecting who will benefit from hemostatic therapy has been demonstrated using DDAVP (52). This compound increases the release of vWF in patients with end-stage renal failure or those with hemophilia. It has been used in trials in cardiopulmonary bypass patients with mixed success. However, in one study wherein the TEG was used as a method to sort out populations with normal platelet function (MA greater than 50 mm) and those with depressed platelet function (MA less than 50 mm), the patients who had depressed platelet function and received DDAVP had the same chest tube output after surgery as those who had normal platelet function. Those patients with depressed platelet function who did not receive DDAVP had considerably greater chest tube drainage and those patients who had normal platelet function, whether they received DDAVP or not, had reasonable amounts of chest tube output (Fig. 26.7). This type of analysis supports the fact that TEG can be used effectively not only to guide therapy but also to assess platelet function (at least the overall function important to the risk of bleeding). The routine application of TEG coagulation assessment in cardiac surgery has reduced blood utilization by approximately 33% in one study (54). Subsequent to that study, an algorithm for blood replacement has been created based on the TEG and the platelet count and the fibrinogen concentration (Fig. 26.8) (58). By using the TEG, not only can blood product administrations be cut down, but the re-exploration rate, a major cause of morbidity, some mortality, and certainly cost, has been considerably decreased (Table 26.1).

Most anesthesia departments run the TEG systems themselves, and this has been a source of some considerable dissatisfaction and criticism of the technology. The TEG must be critically quality-controlled, and new government regulations state that it must be done every 8 to 24 hours. A bioassay system using plasma with a known concentration of fibrinogen has been published (56). Maintenance of the technology is critical for reliable data acquisition. A cooperative effort with the laboratory medicine department has been published that allows quick data return and all the proper maintenance and quality control of the machines.

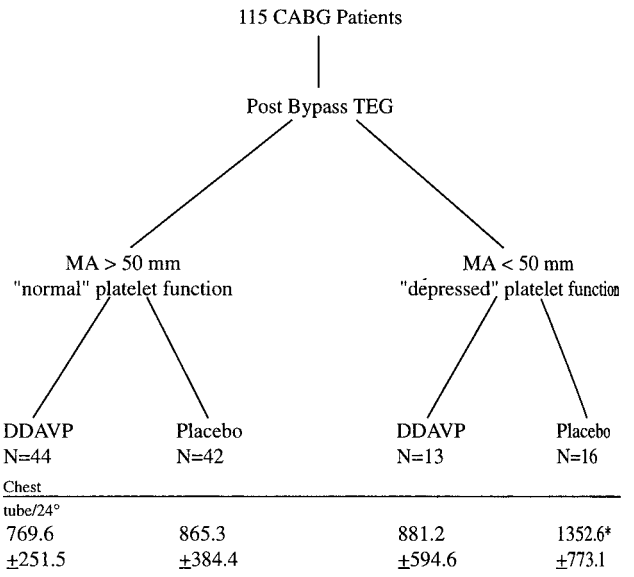


Figure 26.7 The TEG was used to segregate groups of patients with normal or depressed platelet function. Note that patients in the abnormal platelet function group who then received DDAVP had the same (normalized) chest tube output as those in the normal platelet function group. *Significantly different, $P \leq .05$. (Adapted from Mongan PD, Hosking MP. The role of desmopressin acetate in patients undergoing coronary artery bypass surgery. *Anesthesiology.* 1992;77:38–46.)

TEG has been criticized for being slow in giving data; however, if the MA is the most important piece of information, then it can be obtained usually within 10 to 15 minutes, especially with the use of kaolin activator. The use of tissue factor activator yields the MA in 5 minutes or less, but does not yield valuable information for the R and the K time since it accelerates past these steps in coagulation. Another approach to obtaining timely and predictive data has been to reverse heparin with either heparinase or protamine while patients are still on cardiopulmonary bypass; this allows one to guide therapy before separating from cardiopulmonary bypass and to order appropriate blood products in a timely fashion.

The TEG is the best predictor of trace amounts of heparin. It also is the best test for overall hypercoagulability. Several articles show that it follows hypercoagulability after surgery well (70–72). Large studies are necessary to demonstrate whether it can predict patients at risk for pulmonary emboli, graft thrombosis, and other hypercoagulable catastrophes (myocardial infarction and stroke).

The Sonoclot (Sienco, Denver, CO) is a similar device to the TEG in that it assesses whole blood coagulation function as it goes from a liquid to a gel (56). It uses a cup with a suspended piston warmed to 37°C; however, the piston in this system vibrates up and down rapidly and the impedance to vibration is measured. As clot forms from the wall of the cup to the piston, the impedance to vibration increases. Essentially, this system provides a continuous assessment of viscosity. Viscosity and clot strength are related, but one might be more easily convinced that clot strength is the physical force that is necessary to stop capillary bleeding. A Sonoclot signature has been described (Fig. 26.9), and some variations with expected coagulopathies have also been described. The Sonoclot signature has several inflection points, and the time to these inflection points and the height of the tracing at these inflections can be measured. What those inflection points mean in terms of actual biological clot function is not known. Some authors have ascribed certain platelet-mediated events to these inflection points, but scientific corroboration has not been forthcoming. There are also no widely published normals for when and at what height these inflection points should occur.

The Sonoclot does appear to follow changes in coagulation with cardiopulmonary bypass. However, much less research has been conducted with Sonoclot than with TEG, and therefore we simply know less about what factors affect the changes in clot viscosity compared with TEG.

Presently, we are learning more about the basic science of what factors contribute to the whole blood clot strength. Development is underway to produce other whole blood viscoelastic clot-monitoring technologies. We have certainly learned from the TEG that clot strength is a valuable parameter. The use of these data along with other coagulation data (fibrinogen and platelet number) seems to be useful.

Thromboelastography Modifications

Since the MA is a function of the platelet-fibrinogen interaction, a reduction in the MA can be accomplished by the addition of potent GPIIb–IIIa receptor blockade to the assay (59). The resultant MA, in the presence of excessively high GPIIb–IIIa receptor blockade, is primarily due to the fibrinogen concentration and the strength of fibrin alone. This value (called MA_f) correlates strongly with plasma fibrinogen concentration (60).

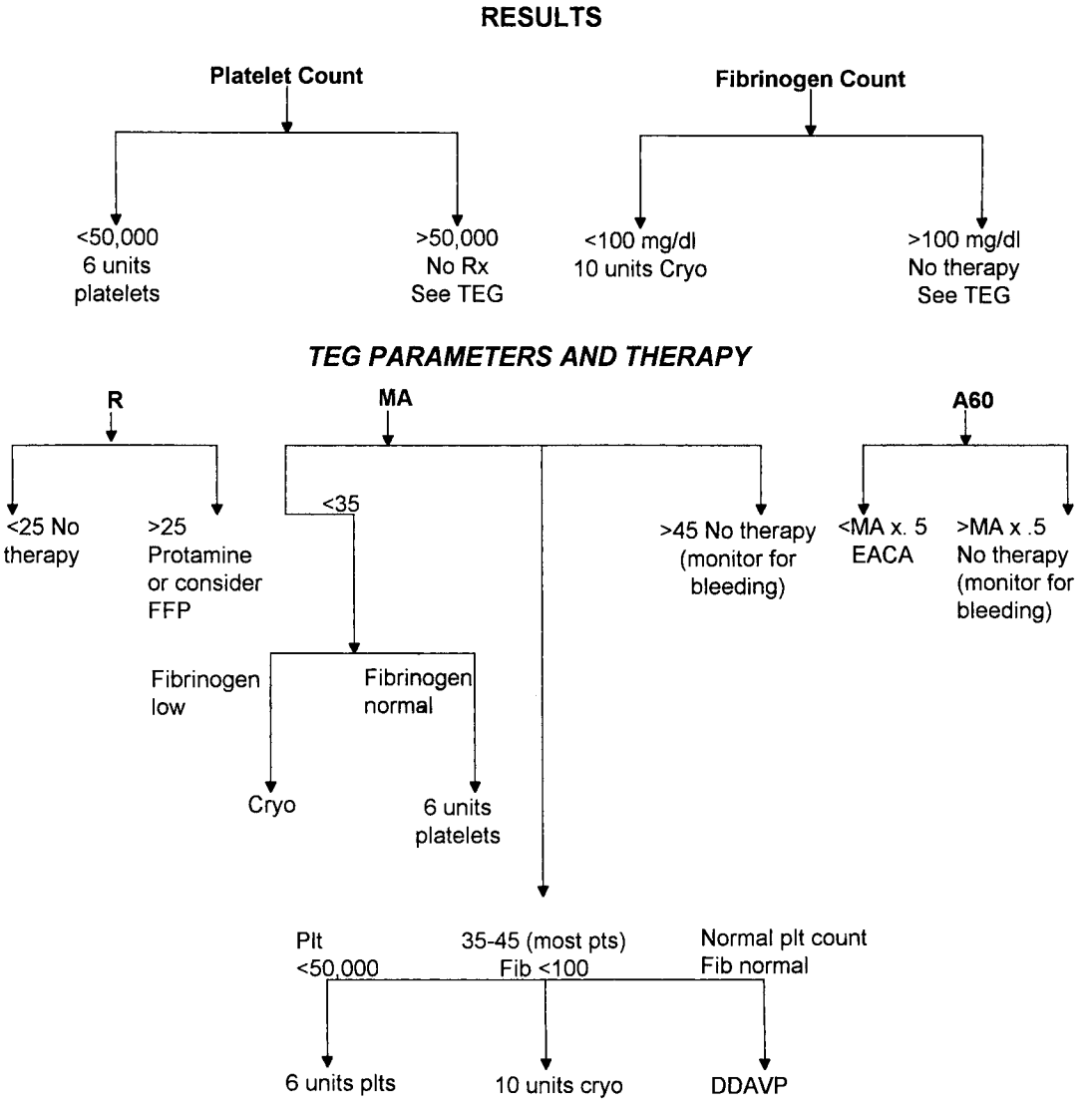
The thienopyridine ADP-receptor blockers, clopidogrel and ticlopidine are widely used in cardiovascular medicine. The ability to measure the platelet defect induced by these drugs is difficult unless sophisticated laboratory techniques such as ADP-aggregometry are used. Aggregometry yields accurate results, however, it is not readily available in the perioperative period as a point-of-care test. Native TEG analysis does not measure the thienopyridine-induced platelet defect because the formation of thrombin in the assay has an overwhelming effect on the development of the TEG MA. A modification of the TEG removes thrombin

Algorithm - Transfusion Guidelines for CPB Patients

Order after Cross Clamp Removal on Bypass

1. Plt count, Fibrinogen & TEG with protamine titration in vitro

All samples tubed to Lab Medicine and order STAT (tube station J-9)



If bleeding develops on entry to ICU:
ACT, TT repeat Plt, Fib, TEG (normal No protamine titration)

Figure 26.8 The algorithm based on TEG, platelet count, and fibrinogen concentration. This algorithm, although used largely for cardiac surgery, should be universally applicable to other surgeries. (Reprinted by permission from Spiess BD. Coagulation dysfunction after cardiopulmonary bypass. In: Williams JP, ed. Postoperative management of the cardiac surgical patient. New York: Churchill Livingstone; 1996:175–197.)

TABLE 26.1
CHANGES IN BLOOD UTILIZATION AND TRANSFUSION BEFORE AND AFTER TEG-GUIDED THERAPY

Transfusion Practice per Surgical Case Type[a]	Group 1 (N = 488)	Group 2 (N = 591)	p
CABG (%)			
Total	87.6	77.7	.001
RBC	84.5	73.1	.001
Plt	57.2	42.7	.001
FFP	31.6	19.6	.001
Cryo	4.5	3.3	.392
Open ventricle or complex (%)			
Total	82.7	81.1	NS
RBC	79.7	76.4	NS
Plt	64.7	64.9	NS
FFP	48.1	46.6	NS
Cryo	11.28	18.9	NS
Mediastinal Reexploration Rates[b]	**Group 1 (N = 488)**	**Group 2 (N = 591)**	**p**
Mediastinal reexploration (n)	28	9	0.0001
Total %	5.7	1.5	
CABG			
Number	16/355	6/443	0.007
Percent	4.5	1.4	
Complex			
Number	12/133	3/148	0.009
Percent	9.0	2.0	

[a] Overall decreases in blood utilization were made because of changes in the needs for transfusion in CABG patients. Open ventricle procedures did not change during this time.
[b] The use of TEG-guided therapy and decision making (reexploration of the mediastinum) has influenced both blood utilization and reoperation rates.
CABG, coronary artery bypass graft; RBC, red blood cell count; Plt, platelet; FFP, fresh frozen plasma; cryo, cryoprecipitate; NS, not significant. (Adapted from Spiess BD, Gillies BSA, Chandler W, et al. Changes in transfusion therapy and reexploration rate after institution of a blood management program in cardiac surgical patient) (54).

from the assay and studies a nonthrombin clot, strengthened by the addition of ADP. Figure 26.10 depicts the different signature TEG tracings that are used to calculate the platelet contribution to MA when a platelet inhibitor is present. This assay was specifically created to measure the platelet inhibition by ADP antagonists such as clopidogrel. It is commercially referred to as the "Platelet Mapping Assay". The MA_{kh} is the maximal activation of

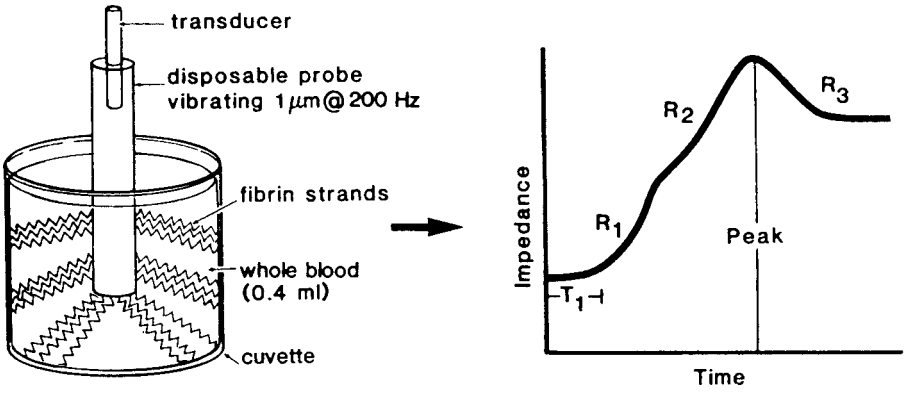


Figure 26.9 The Sonoclot analyzer uses a vertically vibrating probe lowered into a stable cuvette. It tests viscosity over time, and the typical signature is shown with multiple inflection points as viscosity increases. (Reprinted by permission from Tuman KJ, Spiess BD, McCarthy RJ, et al. Comparison of viscoelastic measures of coagulation after cardiopulmonary bypass. *Anesth Analg.* 1989;69:69–75.)

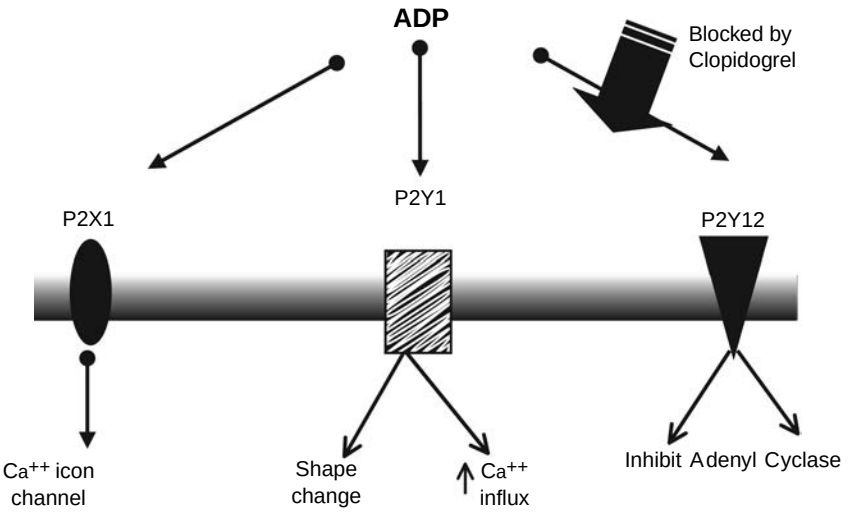


Figure 26.10

platelets and fibrin and is the largest amplitude that can be achieved. The MA_f is the maximal amplitude that is obtained when a thrombin-depleted fibrin clot is formed without a platelet contribution. The MA_{pi} is the MA_f contribution plus the platelet contribution. MA_{pi} is created by adding an activator such as ADP to the MA_f assay (for clopidogrel testing). Only platelets that can be activated by ADP will contribute to the MA_{pi}. The following formula calculates the percent reduction in platelet activity using this assay.

$$100 - [(MA_{pi} - MA_f)/(MA_{kh} - MA_f)] \times 100$$

Clopidogrel, ticlopidine, and even aspirin inhibition, can now be studied at the point of care using this modification (61,62). (This class of drug inhibits platelet aggregation through inhibition of the P2Y12 ADP receptor) (Figure 26.10).

Hemodyne: Platelet–Mediated Force Transduction

An instrument that measures the force developed by platelets during clot retraction has been shown to be directly related to platelet concentration and function (Hemodyne) (63). The apparatus consists of a cup and a parallel upper plate. The cup is filled with blood or the platelet-containing solution, and the upper plate lowered onto the clotting solution. Clot forms and adheres to the outer edges of the cup and to the plate above. A thin layer of oil is deposited onto the surfaces that are exposed to air. The upper plate is coupled to a displacement transducer that translates displacement due to platelet retraction into a force. Using this instrument, investigators have shown that high heparin concentrations completely abolish platelet force generation (64). Furthermore, the concentration of protamine required to reverse the anticoagulant effects of heparin is not sufficient to reverse these antiplatelet effects. The antiplatelet effects of protamine alone have also been evaluated using this monitor.

Fluorescence Flow Cytometry

Fluorescence flow cytometry in the clinical laboratory has provided a sensitive and specific means for assessing etiologies of platelet dysfunction. Disadvantages of the in vitro assays, such as shear-induced stress and clot retraction measurements, are that they represent nonspecific markers of platelet defects. The measure of specific serum markers of platelet activation, such as β–thromboglobulin and PF4, can be performed; however, plasma collection techniques for these tests are cumbersome and the assays are often affected by other metabolic functions. Aggregometry is only a semiquantitative process and requires a high concentration of platelets for its optimal performance.

Flow cytometry is ideal for the detection of low concentrations of specific proteins within a large population of cells. These proteins may either be static portions of the platelet surface or dynamic products of platelet activation. The platelet release reaction enables specific integrin proteins, which are a part of the platelet alpha granule membrane, to incorporate themselves into the platelet surface membrane through a mechanism analogous to exocytosis. A portion of the GPIIb–IIIa receptor is also a protein of the alpha granule membrane that becomes exposed on the

TABLE 26.2
PLATELET DISORDERS AND HEMOSTASIS TESTING AVAILABLE

Pathophysiology	Etiology	Disorder	Testing Available
Absent GPIb	congenital	Bernard Soulier	Flow Cytometry, Bleeding time, PFA-100
Absent GPIIbIIIa	congenital	Glanzmann's thrombasthenia	Flow Cytometry, Aggregation, Ultegra, TEG
vWF	congenital	vWD	Bleeding time, PFA-100
Alpha granule depletion	congenital	Gray Platelet Syndrome	Flow Cytometry, Aggregation
COX inhibition	Drug Therapy	Aspirin ingestion	Aggregation, Bleeding time, PFA-100, modified TEG
ADP P2Y12 inhibition	Drug Therapy	Clopidogrel ingestion	Aggregation, Bleeding time, modified TEG
GPIIbIIIa blockade	Drug Therapy	Abciximab	Aggregation, Flow Cytometry, Ultegra
Increased NO	Drug Therapy	Nitroglycerin	Aggregation, Flow Cytometry

GP, glycoprotein; vWD, Von Willebrand's disease; vWF, Von Willbrand factor; TEG, thromboelastography.

surface membrane of the platelet in response to platelet activation. Flow cytometry allows for the detection and quantification of many of these surface membrane constituents as a result of immunofluorescent innovations (2).

Flow cytometry techniques have been enhanced by the development of specific monoclonal antibodies, which recognize antigens on the platelet (or white blood cell) surface. Antibodies developed are so specific that different ligand binding sites can be measured on the same GPIIb–IIIa molecule that characterize different phases of receptor activation. Some of the epitopes for which monoclonal antibodies have been developed include markers of platelet activation, the activated GPIIb–IIIa complex, and the GPIb receptor (13,17). A large number of monoclonal antibodies are available for identification of specific platelet ligand-binding sites. The technique of flow cytometry can be performed using whole blood or platelet-rich plasma. The fluorescent-labeled monoclonal antibody directed against a specific platelet membrane protein is quantified by the flow cytometer, which is an instrument equipped with a laser or a light source of a specific excitation wavelength. Light scatter data are collected that help to differentiate platelets from other cellular particles. Fluorescent antibody detection is expressed as percent of the total number of particles or as fluorescence intensity. (See Table 26.2 for a variety of different platelet disorders and a number of different platelet function tests available to measure platelet function.)

In the cardiac surgical arena, flow cytometry has aided in diagnosing the disorders of platelet function induced by cardiopulmonary bypass and protamine administration (65,66). Kestin et al. (29) used flow cytometric techniques to study the effects of CPB on the in vivo time-dependent upregulation of P-selectin in blood emerging from a bleeding wound. They showed that P-selectin expression is depressed after heparinization and during CPB and recovers at approximately 2 hours after the conclusion of CPB. In contrast, in vitro activation of CPB blood with the platelet agonist phorbol myristate acetate did not reveal this depression of P-selectin expression at any time point. Using another platelet activator (thrombin receptor agonist peptide) and flow cytometry, others did not demonstrate depression of P-selectin expression early in CPB, but did so after 90 minutes of CPB and after protamine administration (67).

Much uncertainty still exists regarding GPIb receptor modulation in response to CPB. Using flow cytometry, George et al. (2) found a modest reduction in platelet surface GPIb during CPB. However, a subsequent study by van Oeveren (68)confirming a reduction in GPIb subjected the platelets to centrifugation and processing techniques that may have induced in vitro artifactual platelet activation. Kestin et al. (29) employed monoclonal antibodies to many epitopes expressed on GPIb and concluded that expression of this receptor is not reduced during CPB.

Monoclonal antibodies are available that bind to the GPIIb–IIIa fibrinogen binding site and others are available that recognize receptor-bound fibrinogen. Flow cytometric techniques have also helped to characterize the mechanisms of action of several pharmacologic agents that have shown hemostatic potential in the perioperative period (69).

THE PLATELET RESPONSE TO AGONIST

HemoSTATUS

The qualitative measure of platelet function, at the bedside, remains an elusive challenge. This stems from the complex nature of platelet activity and the multitude of pathways available for testing platelet reactivity. HemoSTATUS (Medtronic Inc., Parker, Colo.) is a point-of-care platelet function assay that utilizes the Hepcon monitoring system to measure platelet reactivity. A six-channel cartridge measures the heparinized kaolin-activated ACT without platelet activator (channels 1 and 2), and with incrementally increasing

doses of platelet-activating factor ([PAF] channels three to six). The ACT of the PAF-activated channels will be shortened due to the ability of activated platelets to speed coagulation. The respective doses of PAF in channels three through six are 1.25 nM, 6.25 nM, 12.5 nM, and 150 nM. For each of channels three through six, the degree of shortening of the ACT as a ratio to the ACT without PAF is the clot ratio and is calculated as a $1 - (ACT_{activated}/ACT_{control})$. The maximal clot ratio is the clot ratio for channel six that was derived using blood from normal volunteers. A comparison of the patient clot ratio to the maximal clot ratio (derived from normal volunteers) yields a comparative measure of platelet function, termed the percent of maximal platelet function.

An initial investigation of HemoSTATUS in cardiac surgical patients was performed by Despotis et al. (70). The authors studied 150 patients and conducted multivariate analyses to evaluate the relationship between postoperative blood loss and multiple demographic, operative, and hemostatic measurements (70). They demonstrated a significant correlation between HemoSTATUS measurements upon arrival in the intensive care unit (ICU) and 4 hour postoperative mediastinal tube drainage ($r = -0.85$, channel 5; $r = -0.82$, channel six). Using receiver operating characteristic (ROC) curves for the detection of excessive mediastinal tube drainage, the accuracy of a number of hemostasis assays was measured. The highest predictability for bleeding was found in both the channel five clot ratio and the bleeding time. The PT, aPTT, and platelet count had much lower predictive value. HemoSTATUS-derived clot ratios also had the capability to detect enhanced platelet function after the administration of pharmacologic platelet therapy (desmopressin acetate), and after the transfusion of platelet concentrates. Subsequent investigations in cardiac surgical patients have confirmed a significant yet weak correlation of HemoSTATUS with postoperative bleeding, but have not found this test superior to TEG or routine coagulation tests in its predictive value (71).

Validation studies have been performed in order to compare the assessment of platelet reactivity using HemoSTATUS to that measured by fluorescence flow cytometry. Using each patient's baseline platelet function as the control, the percent reduction in platelet function at multiple time points during cardiac surgery was compared using the two methodologies. Both tests reflected a similar degree of platelet dysfunction at the time points 90 minutes into CPB, after protamine, and at ICU arrival. Differences in the type of assay and the type of platelet activators used (thrombin peptide versus PAF) may have accounted for the inability of the tests to correlate with each other at all of the time points studied (67).

Ultegra (Accumetrics, San Diego, Calif.), or rapid platelet function assay is a point-of-care monitor that was designed specifically to measure the platelet response to a thrombin receptor agonist peptide (TRAP). This technology using an adjunctive cartridge containing ADP, was recently approved by the U.S. Food and Drug administration for use as a platelet function assay for measuring the platelet defect of clopidogrel. This activation process is specific for the P2Y12 receptor which is the ADP receptor blocked by thienopyridine therapy (Figure 26.10). In whole blood, it measures activation-induced platelet-agglutination of fibrinogen coated beads using an optical detection system. Because of the importance of the GPIIbIIIa receptor in mediating fibrinogen-platelet interactions, the Ultegra has been especially useful in accurately measuring receptor inhibition in the invasive cardiology patients receiving GPIIbIIIa inhibiting drugs (19,72). The platelet inhibition measured by Ultegra has been demonstrated to correlate inversely with adverse outcomes after percutaneous coronary intervention (73).

The Hemostatometer has been more recently renamed the Clot Signature Analyzer (CSA, Xylum, Scarsdale, NY). Whole blood is maintained under a constant driving pressure of 60 mm Hg as it is forced out into a synthetic vessel. The pressure distally in the vessel is monitored. The tubing of this synthetic vessel is perforated and the distal pressure drop is measured. The time to restoration of this distal pressure will be a function of development of a platelet plug. Thus the time for initial closure is a measure of platelet function. A subsequent time is measured and that is the time to complete pressure loss due to complete vessel occlusion. This clot will be the result of coagulation and clot formation and the time to the second pressure drop is reflective of coagulation function. Another chamber of this device contains a collagen-coated fibril upon which platelets adhere and form a plug. A similar pressure measurement technique indicates the formation of a platelet thrombus. This point-of-care assay has been used to measure platelet reactivity in high risk patients with atherosclerotic coronary artery disease (74–76). However, in cardiac surgical patients, preoperative platelet reactivity did not have predictive accuracy for bleeding (77). Data evaluating the CSA in the postoperative period to predict bleeding are lacking.

The Platelet Function Analyzer (PFA-100), (Dade Behring, Miami, Fla.) is a monitor of platelet adhesive capacity that is currently approved by the U.S. FDA and is valuable in its diagnostic abilities to identify drug-induced platelet abnormalities, von Willebrand's disease platelet dysfunction, and other acquired and congenital platelet defects (78,79). The test is conducted as a modified in vitro bleeding time. Whole blood is drawn through a chamber by vacuum, and is perfused across an aperture in a collagen membrane coated with an agonist (epinephrine or ADP) (80). Platelet adhesion and formation of aggregates will seal the aperture,

thus indicating the closure time measured by the PFA-100 (81). In cardiac surgical patients, the preoperative PFA-100 closure time significantly correlated with postoperative blood loss ($r = 0.41$, $p = 0.022$) (82). However preliminary evidence with post-CPB sampling and with in vitro addition of glycoprotein IIbIIIa inhibiting drugs suggests that these closure times may exceed those measurable using standard testing with the PFA-100 (83).

"Platelet Works" Ichor (Array Medical, Somerville, NJ) is a test that utilizes the principle of the platelet count ratio to assess platelet reactivity. The instrument is a Coulter counter that measures the platelet count in a standard EDTA-containing tube. Platelet count is also measured in tubes containing the platelet agonists: ristocetin, ADP, epinephrine, collagen, or thrombin. Addition of blood to these agonist tubes causes platelets to activate, adhere to the tube, and to be effectively eliminated from the platelet count. The ratio, of the activated platelet count to the nonactivated platelet count, is a function of the reactivity of the platelets. Early investigation in cardiac surgical patients indicates that this assay is useful in providing a platelet count, and that it is capable of measuring the platelet dysfunction that accompanies CPB (84).

It is essential to understand the complex array of hemostatic insults that occur as a result of extracorporeal circulation before selecting an appropriate platelet function monitor during cardiac surgery. Even in hemostatically normal individuals, CPB induces a heparin effect, platelet dysfunction, fibrinolysis, and coagulation factor defects for which there are many clinical laboratory tests available for accurate diagnoses. With the recent increase in prescription of antithrombotic (84) platelet inhibitors, the hemostatic defect after CPB is even more pronounced. This chapter has introduced the basic principles of hemostasis and the utility of many commonly used monitors for detecting disorders of the coagulation cascade, platelet function, and fibrinolysis. Additionally, an increased emphasis on health care economics has created a milieu in which patients have a rapid transit time through the cardiac operating room with minimal exposure to allogeneic blood products. Prophylactic measures such as heparin-bonded circuitry and antifibrinolytics have reduced the actual incidence of microvascular bleeding in this population. However, when microvascular bleeding does occur, rapid diagnosis and therapeutic intervention are made possible by point-of-care hemostasis testing, which can take place directly in the operating theater. If on-site testing is not available or does not provide sufficient timely information regarding the patient's coagulation defect, transfusion therapy for cardiac surgical patients will remain indiscriminate and empiric, at best.

SUMMARY

Coagulation function is dependent on the action of the protein cascades and the surface ligands of platelets, leading to the eventual formation of a gel that is in the final analysis an interaction of platelets and fibrin. Coagulation monitoring is complex, with a large number of potential in vitro studies that can be performed on any given blood sample. With a rational approach focused on the vital interaction of platelets and fibrin, it is now possible to perform timely coagulation monitoring that has predictive value toward patient hemorrhage. In the future, creative solutions, creation of algorithms, and possibly new technologies should be helpful in following coagulation changes in the perioperative period.

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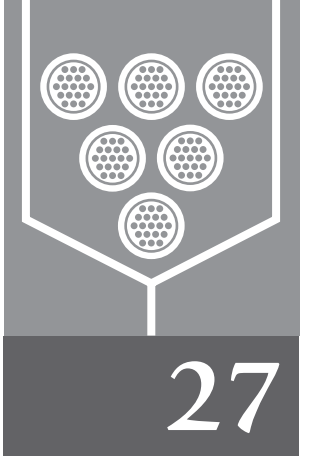

27

Surgery in Patients with Acquired Platelet and Clotting Deficiencies

Richard K. Spence ***Andrew Green***

The preceding chapter discussed congenital clotting disorders; this chapter deals with the increasingly common problem of acquired platelet and coagulation disorders. The introduction of agents that affect various steps in platelet and coagulation function warrant a discussion of their impact on the surgical patient.

The normal platelet count ranges from 150,000 to 400,000 with the exact limits of normal depending upon technique and laboratory. Decreased production, increased destruction, or both may cause *thrombocytopenia*, i.e., a decrease in the number of circulating platelets. An extensive array of conditions may decrease the platelet count, particularly in critically ill patients (Table 27.1). Decreased platelet production occurs when functioning marrow is replaced by tumor, leukemic cells, or fibrosis and in response to myelosuppressive drugs and radiation. Several drugs and toxins exhibit a selective and generally temporary effect on platelet production. Chronic alcohol ingestion causes thrombocytopenia in some patients, apparently by a direct toxic effect on megakaryocytes, and rebound thrombocytosis may accompany alcohol withdrawal. Other drugs that can cause thrombocytopenia include thiazide diuretics, estrogens such as DES, and interferon.

Bone marrow examination will reveal a normal or increased number of megakaryocytes when thrombocytopenia is the result of increased platelet destruction. Thrombopoietin levels vary and are not generally useful as a diagnostic criterion (1). Immunologically mediated platelet destruction, usually caused by an IgG-type antibody, occurs in idiopathic or autoimmune thrombocytopenic purpura, posttransfusion purpura, and heparin-induced thrombocytopenia (2). Consumption of platelets and other clotting factors results in thrombocytopenia in disseminated intravascular coagulation (DIC). Platelet membranes provide a surface on which elements of the coagulation cascade form enzyme complexes that culminate in the formation of thrombin. In addition, α-granules contain significant amounts of some clotting factors, including 20% of factor V. Factor Va derived from α-granules may be more significant for hemostasis than serum factor Va (as evidenced by studies of individuals deficient in one or the other). Patients lacking in serum factor V, but having adequate platelet factor V, have minimal bleeding problems. Defects in platelet membrane receptors have been identified and are known to produce predictable alterations in hemostasis.

In Glanzmann's thrombasthenia, platelet glycoprotein IIb/IIIa is deficient or abnormal. Platelet aggregation with and binding to fibrinogen during clot formation is, therefore, impaired. Characteristically, these patients have a prolonged bleeding time, absent clot retraction, and no demonstrable platelet aggregation in response to any agonist (3). Bernard-Soulier syndrome platelets have a deficiency in glycoprotein Ib, V, and IX. Because glycoprotein Ib binds platelets to the subendothelium via von Willebrand factor, platelet adhesion is impaired. Platelets are large, and moderate thrombocytopenia is often present. Ristocetin-induced platelet agglutination is decreased (similar to the defect observed in von Willebrand disease) and this cannot be corrected by addition of von Willebrand

TABLE 27.1
CONDITIONS AND DRUGS PRODUCING THROMBOCYTOPENIA

Conditions

- Bone marrow replacement by tumor, leukemic cells, or fibrosis and in response to myelosuppressive drugs and radiation.
- Chronic alcohol ingestion.
- Uremia.
- Idiopathic or autoimmune thrombocytopenic purpura.
- Posttransfusion purpura.
- Heparin-induced thrombocytopenia (HIT).

Drugs

- Antimicrobials
  - Antimony containing drugs
    - Stibophen
    - Sodium stibogluconate
  - Cephalosporins
    - Cephamandazole
    - Cefotetan
    - Ceftazidime
    - Cephalothin
  - Ciprofloxacin
    - Clarithromycin
    - Fluconazole
    - Fusidic acid
  - Gentamicin
    - Nilidixic acid
    - Penicillins
      - Ampicillin
      - Apalcillin
      - Methicillin
      - Meziocillin
      - Penicillin
      - Piperacillin
    - Pentamidine
    - Rifampin
    - Sulpha group
      - Sulfamethoxazole
      - Sulfamethoxypyridazine
      - Sulfisoxazole
    - Suramin
    - Vancomycin
- Anti-inflammatory drugs
  - Acetaminophen
  - Salicylates
    - Aspirin
    - Diflunisal
    - Sodium amiosalicylate
    - Sulfasalazine
  - Diclofenac
  - Fenoprofen
  - Ibuprofen
  - Indomethacin
  - Meclofenamate
  - Mefanamic acid
  - Naproxen
  - Oxyphenybutazone
  - Phenylbutazone
  - Piroxicam
  - Sulindac
  - Tolmetin
  - Gold salts
- Cardiac medications and diuretics
  - Digoxin
  - Digiitoxin
  - Amiodarone
  - Procainamide
  - Alprenolol
  - Oxprenolol
  - Captopril
  - Diazoxide
  - Alpha-methyldopa
  - Acetazolamide
  - Chlorothiazide
  - Chlorthalidone
  - Furosemide
  - Hydrochlorothiazide
  - Sprinolactone
- Benzodiazepines
  - Diazepam
- Anti-epileptic drugs
  - Carbamazepine
  - Phenytoin
  - Valproic acid
- H2 Antagonists
  - Cimetidine
  - Ranitidine
- Sulfonylurea drugs
  - Chlorpropamid
  - Glibenclamide
- Iodinated contrast agents
- Retinoids
  - Isotretinoin
  - Etretinate
- Antihistamines
  - Antazoline
  - Chlorpheniramine
- Illicit drugs
  - Cocaine
  - Heroin
  - Quinine contaminants
- Antidepressants
  - Amitriptyline
  - Desipramine
  - Doxepin
  - Imipramine
  - Mianserine
- Miscellaneous drugs
  - Tamoxifen
  - Actinomycin-D
  - Aminoglutethimide
  - Danazole
  - Desferrioxamine
  - Levamizole
  - Lidocaine
  - Morphine
  - Papaverine
  - Ticlopidine
  - Interferon
  - Platelet glycoprotein (GP)IIb/IIIa inhibitors

Available at: http://medicineworld.org/physicians/hematology/thrombocytopenia.html.

factor. This rare autosomal recessive disorder may cause severe, even fatal, mucocutaneous bleeding (3).

Acquired platelet abnormalities are another common cause of bleeding disorders in surgical patients. These can be either quantitative defects secondary to either increased destruction, decreased production of platelets, or qualitative defects as seen in uremia. The platelets count identifies a quantitative deficiency. If the count is greater than 50,000, it is usually safe to proceed with surgery without significant risk of increased bleeding, depending on the surgical procedure itself. Prophylactic replacement of platelets is generally done at levels less than 5,000 to 20,000 to prevent spontaneous bleeding, although cookbook approaches to therapy are generally to be discouraged.

The American Society of Anesthesiologists Task Force on blood component therapy report issued in 1994 presented five recommendations for the use of platelet transfusion (4).

1. Prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction, e.g., ITP.
2. Prophylactic platelet transfusion is rarely indicated in surgical patients with thrombocytopenia due to decreased platelet production when the platelet count is greater than 100×10^9 per liter and is usually indicated when the count is below 50×10^9 per liter. Patients with intermediate platelet counts (50 to 100×10^9 per liter) should be treated based on their risk of bleeding.
3. Surgical and obstetrical patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50×10^9 per liter and rarely require therapy if greater than 100×10^9 per liter. With intermediate platelet counts of 50 to 100×10^9 per liter, the decision to treat should be based on the patient's risk for more significant bleeding.
4. Vaginal deliveries or operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50×10^9 per liter.
5 Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding. Platelet transfusion may be used when profound thrombocytopenia complicates surgical hemostasis. It is estimated that one unit of platelet concentrate will increase the platelet count by a 5 to 10×10^9 per liter. The usual dose chosen is one unit of platelet concentrate per 10 kg body weight. Platelet transfusions are contraindicated in patients with thrombotic thrombocytopenic purpura and hemolytic uremic syndrome since platelets tend to worsen these syndromes. They are less effective in correcting thrombocytopenia secondary to ITP, hypersplenism, DIC, antiplatelet antibodies, and sepsis (4).

Abnormal bleeding can also be caused by platelet dysfunction even when platelet counts are normal. Etiologies include certain drugs containing acetosalicylic acid (aspirin) or other nonsteroidal anti-inflammatory agents, glycoprotein IIb/IIIa platelet inhibitors, and certain diseases such as vWD and renal failure with uremia. The exact cause of the defect in renal failure is still poorly understood and is thought to be multifactorial in origin. The knowledge that the bleeding tendencies improve with hemodialysis lends support to the theory that antiplatelet toxins may contribute to the effect (6).

Acetosalicylic acid (ASA) and nonsteroidal anti-inflammatory agents produce a mild systemic hemostatic defect by inhibiting normal platelet. Compounds containing ASA permanently inactivate cyclooxygenase (COX), while nonaspirin NSAIDs reversibly block COX. Both classes of drug cause platelet dysfunction by inhibiting the formation of thromboxane A2, a platelet activating and vasoconstricting eicosanoid (7). Opinions vary on whether or not these drugs should be discontinued before elective surgery (8-10). The expert recommendations of the French Society of Anesthesiology and Intensive Care published in 2002 counsel against the practice of withdrawing antiplatelet agents before surgery because of reports of an increased incidence of myocardial infarction in patients so treated. They do not recommend stopping ASA, clopidogrel, or ticlopidine unless there is a definite risk of increased intraoperative bleeding or anticipated difficulty in maintaining surgical hemostasis. Platelet transfusion should only be given when overt and uncontrollable bleeding is observed. Antiplatelet treatment should be resumed as soon as possible after surgery (11). Elective surgery that permits control of microvascular bleeding or oozing with cautery or other means can be performed safely without stopping these drugs. However, we recommend stopping these agents at least 1 week before performing procedures in which hemostasis cannot be visually confirmed, e.g., endoscopic treatment of the genitourinary and GI tracts, sphincterotomy, etc (12). Surgery that carries a high risk of bleeding, i.e., cardiac and vascular surgery, may warrant discontinuing therapy. Finally, these drugs should be discontinued in the Jehovah's Witness patient.

The advent of platelet inhibiting drugs used in conjunction with coronary angioplasty has created a new risk of drug-induced bleeding in the surgical patient. The thieopyridines, ticlyridin and clopidogrel, inhibit ADP-induced platelet aggregation. Abciximab, eptifibatide, and tirofiban inhibit Glycoprotein IIb/IIIa receptors. The former are oral preparations; the latter are given intravenously during angioplasty procedures. An analysis of 18,821 patients who underwent coronary artery interventions showed a twofold increase in the risk of subsequent bleeding in those receiving G IIb/IIIa inhibitors, which provides a baseline for risk assessment in the surgical patient (13). The risk of bleeding during emergency surgery after failed intervention is both drug-dependent and time-dependent. Cheng et al. (14) found no increase in risk with eptifibatide even when surgery was performed within 2 hours of drug administration. However, both the risk of bleeding and the need for platelet transfusions were increased if surgery was performed up to 12 hours after administration of abciximab. Dyke (15) reported an increased risk of bleeding in similar patients if abciximab had been given within 6 hours of surgery.

If the decision is made to stop clopidogrel before surgery, the drug should be stopped at least 7 to 10 days before elective surgery to allow replenishment of sufficient platelets to facilitate normal coagulation. Interim management with short acting unfractionated or low molecular weight heparin can protect the patient against unwanted thrombosis. Bear in mind that the antiplatelet effect of clopidigrel persists for several days after withdrawal.

Clopidogrel and ASA in combination act synergistically to increase the risk of perioperative bleeding and must be stopped before elective surgery (16).

Intravenous agents have shorter half-lives, but their effects may also persist. Recommended perioperative therapy in patients treated with these drugs is to infuse platelets if bleeding occurs. Unfortunately, this may take many units of platelets to achieve a clinical effect because the drugs have the ability to redistribute from endogenous to exogenous platelets.

ACQUIRED COAGULOPATHIES

Acquired coagulopathies include hepatic and Vitamin K related factor deficiencies, consumptive coagulopathies, e.g., disseminated intravascular coagulation (DIC), anticoagulant overdose, and qualitative or quantitative platelet abnormalities (17). Of the acquired disorders, the most common are drug-related, specifically those caused by medications that interfere with vitamin K and hepatic production of coagulation factors (Tables 27.2 and 27.3). Surgeons should be familiar with the intentional use, mechanisms of action, and means of reversal of warfarin and heparin compounds. Perhaps less well understood or recognized is the effect on coagulation of antibiotics that inhibit the vitamin K carboxylyase enzymes via the N-Methylthiotetrazole sidechain (18). Antibiotics included in this category include the cefalosporins, specifically cefamandole, cefoperazone, and moxalactam. The effect of these drugs is especially apparent in the elderly undernourished patient, who may already have compromised Vitamin K storage. Many herbal "medicines" have an impact on Vitamin K metabolism. One must also be aware of other causes of Vitamin K deficiency including liver failure, obstructive jaundice, and severe malnutrition.

TABLE 27.2
WARFARIN DRUG INTERACTIONS THAT ENHANCE ITS ANTICOAGULANT EFFECT

Antimicrobials
Cephalosporins
Erythromycin
Azole antifungals
Isoniazid
Metronidazole
Quinolones
Trimethoprim-sulfamethoxazole
Quinidine
Anti-inflammatory drugs
NSAIDs
Acetominophen
Anabolic steroids

TABLE 27.3
WARFARIN DRUG INTERACTIONS THAT INHIBIT ITS ANTICOAGULANT EFFECT

Barbiturates	Carbamazepine
Phenytoin (long term Rx)	Rifampin
Nafcillin	Cholestyramine
Griseofulvin	Penicillin
Alcohol	Vitamin E (mega dose)
Amiodarone	Propafenone
Cimetidine	Clofibrate
Disulfuram	Glucagon
Prilosec	Phenytoin
Tamoxifen	Thyroxine
Tolbutamide	

One is likely to encounter iatrogenic bleeding caused by warfarin in the elective surgical setting. Patients taking warfarin should be advised to stop the drug at least 3 days before surgery. Prothrombin time and international normalized ratio (INR) should be measured just before surgery to determine if the anticoagulation has been reversed. Patients at risk for thrombotic events can be safely managed with interim doses of subcutaneous low molecular weight heparin.

The dosage of warfarin is adjusted normally using the PT and INR. Special care must be taken in adjusting warfarin dosage schedules in patients taking medications that enhance or inhibit the effects of warfarin. Warfarin overdose or an elevated PT can be corrected with administration of Vitamin K either orally, IV, IM, or subcutaneously. There are some drawbacks to each of these methods of administration. When given orally, the absorption of Vitamin K is unreliable and the desired dose may not be achieved. Intravenous administration may produce an anaphylactic reaction. Intramuscular injections may provoke bleeding and cause hematomas. The onset of action by vitamin K is longer than that of replacement therapy and its effects persist, making it difficult at times to re-establish anticoagulation. When rapid reversal of anticoagulation produced by warfarin is desired, FFP is the treatment of choice. Repeat infusions should be given every 6 hours to account for the short half-life of factor VII.

Heparin is another common anticoagulant that sometimes leads to surgical bleeding. Heparin's mode of action is multifactorial. It has a major effect on antithrombin III by markedly increasing its ability to neutralize thrombin. When overdoses occur, significant bleeding is uncommon. Stopping the heparin is usually a sufficient response thanks to the drug's short half-life. When rapid reversal of heparin is needed, protamine can be used. The dosage is

determined by the amount of heparin that was given. One mg of protamine neutralizes approximately 100 units of heparin. Protamine should not be given in doses greater than 50 mg because it may cause hypotension and/or anaphylactoid reactions. Careful monitoring of heparin during cardiac and vascular surgery is essential to prevent unwanted bleeding and unnecessary administration of blood components.

VASCULAR HEMOSTATIC DISORDERS

There are a number of disorders that have been classified as vascular hemostatic disorders although they rarely manifest as significant bleeding or thrombotic problems (17). Abnormal circulating proteins may precipitate in the microvasculature, leading to localized thrombosis. These may be monoclonal, such as those produced in multiple myeloma and Waldenstrom's macroglobulinemia or polyclonal, such as those found in the cryoglobulinemias (19,20). They are associated with infectious, autoimmune, and neoplastic disorders. Patients typically present with purpuric skin rash, urticaria, arthralgia, motor sensitive polyneuropathy, and diffuse proliferative glomerulonephritis. Laboratory measurements may show anemia, rheumatoid factor and decreased complement levels as well abnormal populations of paraproteins and/or immunoglobulins (19–22).

Individuals who develop autoantibodies to factor VIII may present with acquired hemophilia. This rare disorder occurs most often in adults in association with an autoimmune disorder or pregnancy (23). The bleeding diathesis in these patients is often severe and life-threatening. This disorder should be suspected in a patient with no history of classic hemophilia with a bleeding disorder, a prolonged partial thromboplastin time (PTT), and a normal prothrombin time. The definite laboratory diagnosis of this disorder includes demonstration of low factor VIII levels in plasma with a high titer of factor VIII inhibitors (7).

Purpuras form another group of vascular hemostatic disorders. Hyperglobulinemic purpura caused by increased gamma globulin levels is similar in its presentation to the disorders described above (24). Henoch-Schonlein purpura is a form of nonthrombocytopenic purpura due to a hypersensitivity vasculitis seen primarily in children. It is usually benign and presents with a variety of clinical symptoms including urticaria and erythema, arthropathy and arthritis, gastrointestinal symptoms, and renal involvement. On rare occasions, patients have life-threatening hemorrhage that requires blood and blood product support (25). Waterhouse-Friedrichsen Syndrome is a condition characterized by the abrupt onset of fever, petechiae, arthralgia, weakness, and myalgias followed by acute hemorrhagic necrosis of the adrenal glands and severe cardiovascular dysfunction. The syndrome is most often associated with meningococcal septicemia but may occur as a complication of sepsis caused by other organisms, including certain Streptococcus species. This disorder may be associated with a prior history of splenectomy (26). Wiskott-Aldrich Syndrome is a rare, cross-linked immunodeficiency syndrome characterized by eczema, thrombocytopenic purpura, and recurrent pyogenic infection. It is seen exclusively in young boys. Typically, immunoglobulin M levels are low and immunoglobulin A and E levels are elevated. Lymphoreticular malignancies are common.

A third group of vascular hemostatic disorders includes those associated with hereditable connective tissue abnormalities and/or vascular malformations. These disorders are considered hemostatic in part because of their predilection for bleeding or thrombosis and the development of consumptive coagulopathies after either hemorrhage or excision (27). Two inherited disorders of connective tissue have major cardiovascular complications, Marfan syndrome and Ehlers-Danlos syndrome type IV (28). Marfan syndrome results from mutations in the FBN1 gene, which encodes fibrillin-1, an extracellular matrix component found in structures called microfibrils. Ehlers-Danlos syndrome type IV results from mutations in the COL3A1 gene, which encodes the polypeptides in type III collagen. Marfan syndrome remains primarily a clinical diagnosis. Biochemical analysis of the amount of type III collagen produced by dermal fibroblasts has proven to be a powerful diagnostic test for Ehlers-Danlos syndrome type IV. The most common manifestations of Ehlers-Danlos Syndrome are hyperextensible skin and joints, skin fragility, and reduced wound healing capability. Collagen disorders are associated with congenital intracranial aneurysms, accounting for approximately 5% of these cases (28). Patients with Ehlers-Danlos syndrome may present with sudden, massive gastrointestinal hemorrhage (30). Freeman et al. (31) reported 95 complications from Ehlers-Danlos Type IV syndrome in 1996. Their series included 45 vascular problems, which included 22 patients with spontaneous intrabdominal hemorrhage. They recommend treatment with nonoperative, i.e., angiographic interventions as a first step, followed by simple vessel ligation. Cavernous hemangiomata and hereditary hemorrhagic telangectasias can be loosely added to this group. Cavernous hemangiomata are vascular tumors composed of large dilated blood vessels, often containing large amounts of blood. They can be found in the skin, in subcutaneous tissues, in many abdominal viscera, particularly the liver, spleen, pancreas, and in the brain (32).

Hereditary hemorrhagic telangiectasia is an autosomal dominant inherited disease associated with various vascular

malformations (33). It is caused by defects of transmembrane protein components of the receptor complex for transforming growth factor beta (TGF beta). Vascular malformations can be found in the pulmonary, spinal, intracerebral, and the hepatic circulation. They vary in size and may be asymptomatic or responsible for hemorrhage, thrombosis, cardiac-insufficiency, portal hypertension, and hepatic encephalopathy secondary to shunting. Hepatic involvement can usually be confirmed with color Duplex scanning. Embolization or ligation of the malformations is the main therapeutic strategy.

The Shwartzman phenomenon is defined as a local or systemic vasculitis caused by a two-stage reaction. An initial exposure to endotoxin produces intravascular fibrin thrombi whose clearance results in reticuloendothelial blockade. This prevents the clearance of thrombi generated by a second exposure to endotoxin, polyanions, glycogen, or antigen/antibody complexes, which leads to tissue necrosis and/or hemorrhage. In pregnancy gram-negative septicemia during delivery or abortion may serve as the first or provocative encounter (34). The Shwartzman phenomenon is often associated with sepsis, the systemic inflammatory response syndrome (SIRS) and DIC.

SUMMARY

Coagulation can be affected by many congenital and acquired abnormalities, so the physician must be vigilant in preparing a patient for surgery if unexpected and unwarranted bleeding is to be avoided. We have summarized our approach to planning for surgery to help simplify what may appear to be a daunting task (Table 27.4).

TABLE 27.4

PLAN FOR SURGICAL PATIENT WITH INHERITED OR ACQUIRED BLEEDING DISORDER

1) If disorder is acquired, consider delaying surgery until it can be corrected.
2) Preoperative consult with experienced hematologist.
3) Explain risks of surgery and factor therapy in advance.
4) Look for inhibitor antibodies and measure titers.
5) If surgery is for a lesion that occurred because of suboptimal management of the underlying disease, especially hemophilia, maximize preoperative treatment to normalize as much as possible.
6) Avoid any and all aspirin or nonsteroidal anti-inflammatory or platelet inhibiting medications.
7) Schedule surgery for a time period when full laboratory facilities are available on ongoing basis to measure levels, e.g., early in week.
8) Have enough replacement factor for at least 2 weeks available in blood bank.
9) Consider combining major and minor operations, e.g., abdominal and dental surgery.
10) Avoid IM injections in the perioperative period.

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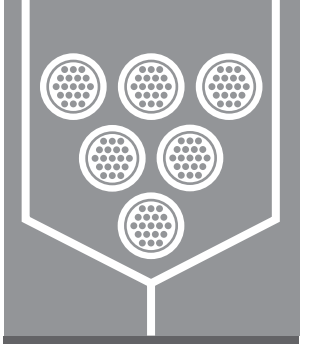

28

Surgery in Patients with Congenital Clotting Deficiencies

Richard K. Spence ***Andrew Green***

A key element of any transfusion avoidance philosophy is the prevention of unsuspected bleeding during elective surgery. There are four crucial elements associated with prevention of bleeding: (a) a thorough history and physical exam with appropriate laboratory data to detect a bleeding disorder that would otherwise go unnoticed, (b) understanding the treatment of bleeding disorders when discovered, (c) meticulous surgical technique, and (d) a comprehensive knowledge of the surgical anatomy prior to surgery. In this chapter we will focus on the first two elements as they relate to congenital clotting deficiencies that can produce abnormal bleeding.

PREOPERATIVE EVALUATION AND TESTING

Preoperative evaluation of any patient begins with a complete history and physical examination. The risk of bleeding during surgery from a congenital clotting deficiency is assessed primarily by past history. The hemophilias appear early in life and should be suspected in a male patient with a history of abnormal bleeding appearing as easy bruising, mucosal bleeding, and bleeding into muscle and joints. History is not as helpful in diagnosing von Willebrand's disease, which may appear for the first time as abnormal bleeding during surgery.

History-taking is most reliable when specific questions are used to determine if a bleeding disorder may exist and to guide subsequent testing. Rapaport (1) has suggested beginning with a simple questionnaire to be filled out by the patient in the waiting room. This would include questions such as: Have you bled for an extended period of time after biting or cutting your lip? Do you develop bruises larger than a silver dollar? Have you had any bleeding problems with previous surgery? If so, please describe them. What medications, including aspirin and other over the counter medicines do you take? And finally, do you have any relatives with bleeding disorders? For example, Factor XI deficiency clusters in patients of Ashkenazi Jewish extraction and should be evaluated in these patients with menorrhagia or an unexplained, prolonged partial thromboplastin time (PTT) (2).

This information is supplemented by the physician's plan for the type of surgery scheduled. Is the patient to have a minor skin incision or a laparoscopic cholecystectomy, where the risks of bleeding and transfusion are minimal? Or, is the procedure scheduled one associated with higher levels of blood loss and transfusion, e.g., abdominal aortic aneurysm repair? Ideally, the individual surgeon will have gathered information about transfusion rates and practices based on his or her own experience.

Based on the results of the history, patients are then divided into four levels (Table 28.1). Simply stated, Level I patients are those undergoing minor surgery with a negative bleeding history. Level II includes patients with a negative bleeding history undergoing major surgery. Level III are high-risk surgery patients and/or those with a history that reveals a possible coagulation defect. Level IV identifies any patient with a known or highly suggestive history of a bleeding coagulopathy who will undergo surgery.

TABLE 28.1
RISK OF BLEEDING BASED ON HISTORICAL DATA

Level	Surgery	Hx Bleeding?	Example
I	Minor	No	Excision of skin lesion
II	Major	No	Abdominal aortic aneurysm repair
III	Major	Yes or no	CABG in pt. with vWF deficiency
IV	Major or minor	Yes	Hernia repair in hemophiliac

Rapaport (1) further recommends specific types of preoperative testing for different levels. For Level I, no laboratory data about coagulation are needed. This category would include dental extractions, removal of smaller skin lesions, etc. He recommends obtaining a partial thromboplastin time (PTT) and platelet count in Level II patients. Level III patients should have a complete blood count (CBC) with platelet count, prothrombin time (PT), PTT, and a bleeding time. For example, Factor XII deficiency may be suspected in a patient with a prolonged activated partial thromboplastin time (APTT), normal prothrombin time (PT), normal bleeding time, and no clinical history of bleeding. Level IV patients receive all the above tests as described for Level III patients. If these tests are negative, one should proceed with further specialized tests to check for specific factor deficiencies, including factor VIII, factor IX, factor XIII, and Von Willebrand's factor. Surgery must be deferred while testing of these patients is done in consultation with a hematologist.

Routine screening of patients using platelet counts, PT, and PTT is to be discouraged for several reasons (2). These tests will not provide the information needed to diagnose a bleeding disorder in the majority of cases. Reliance on negative or normal test results as proof that a patient does not have disorders such as von Willebrand's disease or that a patient will not bleed from aspirin-induced platelet dysfunction is dangerous. Analyses have shown that these tests are not appropriate and only add to the expense of treatment (3,4).

COAGULATION CASCADE

It is helpful to have a basic understanding of the coagulation cascade and the mechanism of clotting in surgery in deciding if a patient has a bleeding disorder. Traditionally, the coagulation cascade was divided into the intrinsic and extrinsic pathways, based on the relationship of factors to either the PT or PTT (5) (Figure 28.1). The intrinsic pathway, which is measured by the PTT, begins with factor XII

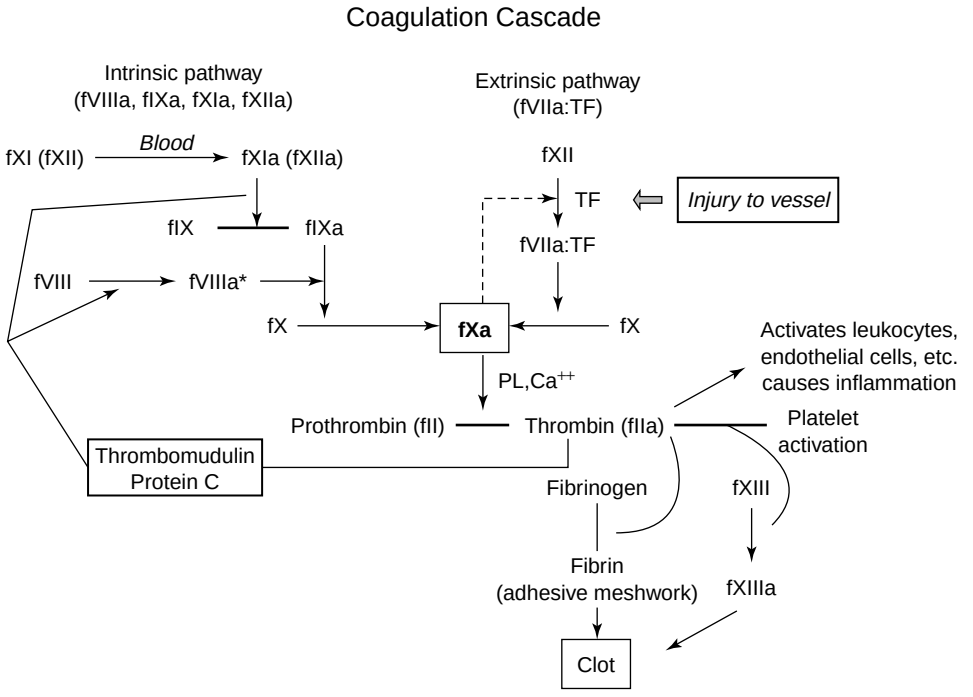

Figure 28.1 The extrinsic and intrinsic coagulation pathways. From Michael Meyer, PhD, Albany Molecular Research, Inc. *Technical Report: Volume 7, No. 64, 2002.*

combining two circulating factors in the blood and then proceeding through Factors XI and IX until the common pathway beginning at Factor X is reached. The extrinsic pathway (measured by the PT) begins with factor VII, which combines with tissue factor in the presence of calcium to activate factor X. Factor X, the first step in the final common pathway, activates the conversion of prothrombin II to activated thrombin II with the aid of factor V. Thrombin converts fibrinogen into fibrin leading to clot formation.

In reality, coagulation is more a combination of protease, calcium, and cofactor interactions on the cell membrane and less a series of specific reactions as depicted by the cascade. It is now thought that the tissue factor (TF) and factor VII pathway is the initiating event of in vivo blood coagulation. The TF-activated factor VII complex is needed to convert factor X from an inactive to an active form. Activated factors VIII and IX catalyze this reaction on cell membranes. Native factor VIII is carried in the circulation in low concentrations bound to von Willebrand factor. Once activated, factor VIII is unstable and must be bound to factor IX. Activated factor XIII acts on fibrin to stabilize the clot. In its absence, the fibrin clot is weakened and wound healing is impaired.

The cell membrane plays an essential role in the coagulation process. Blood vessel injury exposes the subendothelium, which contains a variety of substances including collagen, elastin, and von Willebrand factor. These substances are both potential stimuli of platelet aggregation and initiators of the coagulation process. Knowledge of these interrelationships can help the surgeon understand why certain factor deficiencies are clinically important while others are not. Deficiencies of factors VIII and IX and von Willebrand factor all may produce clinical bleeding because they are essential components of the coagulation reaction. Deficiencies of factors XI and XII will prolong the PTT, but do not typically result in clinical bleeding.

BLEEDING DISORDERS

In the congenital disorders of coagulation, individual clotting factors are produced in decreased numbers or in abnormal forms. These are conventionally grouped according to the factor that is diminished or abnormal (for example, factor VIII in hemophilia A). Factor levels must be significantly below normal before screening tests such as the PT and PTT are prolonged. Affected individuals vary in the severity of bleeding problems, depending on how much of the factor is present or how abnormal it is. For example, in hemophilia A, the PTT remains normal until factor VIII falls below 30% of normal levels (6,7).

Hemophilia A and B and von Willebrand's disease are the most common of the congenital coagulopathies. Hemophilia A is an inherited deficiency in production of factor VIII. Hemophilia B, also known as Christmas disease, is an inherited deficiency of factor IX. Von Willebrand's disease is the most common of all congenital coagulopathies, occurring in 1% to 2 % of the population (6). Rare deficiencies of factors II, V, VII, X, and XIII associated with clinical bleeding have been reported (5). These disorders are rarely diagnosed prior to surgery. All can be treated successfully with fresh frozen plasma to replace the deficient factor.

The Hemophilias

Hemophilia A (Factor VIII deficiency) and hemophilia B (Factor IX deficiency) are both chromosome cross-linked recessive disorders that are expressed in the male offspring of the female carriers. *Hemophilia A*, or classic hemophilia (factor VIII deficiency), is by far the most commonly inherited coagulation disorder, occurring in approximately 1 of 10,000 male births and accounting for 80% of all congenital factor deficiencies (5,7). Hemophilia is usually diagnosed prior to a need for surgical intervention and should be suspected in a male patient with a history of abnormal bleeding including easy bruising, mucosal bleeding, and bleeding into muscle and joints. Any male without a prior diagnosis, suggestive history, and prolonged aPTT should be screened for factors VIII and IX to make a definitive diagnosis prior to surgery. Clinical manifestations correlate with factor VIII levels, which vary from less than 1% in severely affected individuals to as high as 40% in those with mild hemophilia.

Hemophilia B (Christmas disease, named for the first patient studied in detail), or factor IX deficiency was identified when it was observed that blood from one hemophiliac corrected the prolonged clotting time of another patient with hemophilia. The pattern of inheritance and clinical manifestations are similar. Historical and clinical features resemble those in classic hemophilia A, but patients present with fewer symptoms. Severity of bleeding is usually similar in members of a single family. Many patients are asymptomatic until the hemostatic system is stressed by surgery or trauma. Generally, the PT is normal and the PTT is prolonged; however, factor IX activity must be less than 30% of normal for prolongation to occur (7).

Patients with severe hemophilia, which is defined as less than 1% of normal plasma levels of factor VIII or IX (0.01 U per mL or less), are at risk of spontaneous bleeding. Death secondary to intracranial hemorrhage following minimal trauma has been reported in as many as 25% of hemophiliacs (8,9). Moderate hemophiliacs with plasma levels from 1% to 5% (0.01 to 0.05 U per mL) rarely have

spontaneous hemorrhage but do have prolonged bleeding with minor trauma (10). Mild hemophiliacs, those with levels from 6% to 25% (0.05 to 0.30 U per mL) only bleed with significant trauma or surgery (5). Unfortunately, approximately 65% of patients afflicted have severe disease (7).

The treatment of hemophilia has improved greatly over the years from transfusion of whole blood to replace the needed clotting factors to infusion of highly purified, recombinant factor VIII concentrates (11). Unfortunately, sterilized factor VIII concentrates were not available until 1984, and at present, approximately 90% of severely affected multiple transfused hemophiliacs have chronic active or chronic persistent hepatitis. The same percentage is HIV positive (12).

Treatment of hemophilia A depends on the severity of the disease and the specific setting. The goal of therapy simply stated is to increase the deficient factor enough to stop the bleeding. When surgery is necessary in individuals with coagulation disorders, serum factor levels guide replacement therapy. In hemophilia A, factor levels should be brought to 100% before elective surgery and held at 40% of normal until all drains and sutures are out (13). Additional factor replacement at the time of suture removal may be required. In some disorders, wound healing is delayed. This should be anticipated and sutures should be left in for a longer period than usual. Topical hemostatic agents and fibrin glue may be useful but cannot replace meticulous hemostasis (14).

Therapy is rated both by the clinical response and the levels of clotting factors measured posttransfusion. One should not necessarily follow the PT and PTT results because these can be misleading. In someone with known hemophilia A, levels of factor VIII should be 80% to 100% prior to surgery. In a patient with only mild hemophilia, DDAVP, or desmopressin, DDAVP may be used in patients with mild hemophilia A who are scheduled for elective surgery. A dose of 0.3 grams per kilogram is sufficient to increase levels fourfold to fivefold (14–16). DDAVP causes release of endogenous factor VIII from liver sinusoids and endothelial cells, and also releases VWF resulting in a transient increase in factor VIII levels. Because the response is variable it should be monitored (bleeding time and aPTT). In moderate and severe hemophiliacs, there is insufficient factor VIII available to use this approach, so replacement therapy must be used (Table 28.2). Once factor VIII levels have been raised they should be kept at 30% to 50% of normal by transfusing replacement factors every 8 to 12 hours over the next 7 to 10 days postsurgery. The short half-life of factor VIII (approximately 8 hours) mandates repeat measurement to assure that satisfactory levels are maintained (18).

One can use a simple formula for calculating the dose of factor VIII needed to accomplish these goals. For every unit of replacement factor VIII given per kilogram body weight, plasma levels increase by 2%. Therefore, to calculate the needed dose one subtracts the patient's measured factor levels from the desired goal, for example, 100% prior to surgery. The differences then are multiplied by the patient's weight in kilograms. This number is then divided by two, since each unit transfused will raise the plasma levels by 2%. An example is shown in Table 28.3. This same process is then repeated every 8 hours by measuring the patient's factor levels and calculating to maintain the levels 80% to 85% of normal. It is important to note here that these are only general guidelines and total factor replacement needed should be calculated by following the patient's measured factor levels closely.

Heat-treated, concentrated preparations of factor IX are available for patients with hemophilia B, but the dosing is a little different. Calculation of dosage is complicated by loss of 50% of infused factor IX. The exact mechanism is unknown but binding to endothelial cells or movement into intravascular space are suspects. Also, factor IX levels greater than 50% increase the risks of venous and arterial thromboses. For this reason, treatment generally aims at producing factor IX levels of approximately 50% normal (12,19). Factor levels are maintained at 40% for 2 to 3 days, then 20% for 7 to 10 days. When replacing factor IX, once-a-day dosing is all that is necessary because the factor has a half-life of approximately 24 hours. Each unit of factor IX given per kilogram body weight raises plasma levels by only 1%.

Fresh frozen plasma can be used to treat patients with hemophilia B (20). However, these preparations may contain contaminates of factors II, VII, and IX that might cause a hypercoagulable state when transfused in large quantities (21). Simultaneous administration of heparin (5,000 units sub q every 8 hours) may be needed to prevent thrombotic complications. Purified and recombinant factor IX products are preferred when available. Fresh frozen plasma also carries the risk of blood borne disease transmission.

As many as 5% to 35% of patients with hemophilia will develop inhibitors to factor VIII in the form of IgG antibodies (22). High levels of inhibitor will blunt or inhibit the response to replacement therapy. The presence of inhibitors is determined by using the Bethesda assay, performed by mixing the patient's plasma with normal plasma and measuring the decrease in factor levels. A decrease of 50% is equal to one Bethesda unit (22). The number of Bethesda units determines the amount of factor to replace. The effects of these inhibitors can be overcome in one of three ways. If time allows, one can attempt to eradicate the inhibitor by immune tolerance induction. This process relies on the effect of large daily doses of factor VIII given over weeks to months to eradicate the inhibitor. Although

TABLE 28.2
PERIOPERATIVE TREATMENT OF BLEEDING DISORDERS

Hemophilia A—(Factor VIII)

Goal: Raise FVIII to 80%–100%
Approach: FVIII concentrate*. # units = (% X Kg. BW)/2
If inhibitors present:
1) 70–150 U/Kg bolus, then 5–15 U/Kg Qhr or 40 U/Kg plus 20 U/Kg for each Bethesda unit Qhr human FVIII
2) plasmapheresis to remove inhibitor; replace FVIII with porcine or recombinant FVIII
3) recombinant FIX or VII
Goal: Maintain FVIII at 80%–100% for 10–14 days
Approach: same as for preop; reinfuse every 8–12 hrs (or longer if surgery extensive).
Monitor FVIII levels as guide to therapy.
* viral inactivated or recombinant factor VIII concentrate.

Hemophilia B—(Factor IX)

Goals: 1) Factor IX levels to 80%–100%
Approach: 1) FIX concentrate*. # units = % X Kg BW.
2) Use FFP if deficit and surgery minimal
N.B. FIX concentrate may cause thrombosis. Consider adding heparin 5,000 units SQ every 8 hrs.
Goal: Maintain FIX levels at 40%–50% for 2–3 days, then 20% for 7–10 days or longer, depending on response.
Approach: same as preop.
Monitor FIX levels as guide to therapy.
* highly purified viral inactivated factor IX concentrate
von Willebrand's—(vW Factor)
Goals: 1) Raise vWf to 80–100 U/dL
2) replace abnormal vWf 3) raise FVIII as needed
Approach: 1) DDAVP—0.3μg/Kg IV in 20 mL saline over 30 minutes; repeat Q12–24 hrs.
2) if DDAVP failure, use FVIII concentrate using same approach as above
3) replace FVIII as needed
Goals: 1) Maintain vWf at 40 U/dL for 2–3 days or longer as needed
2) maintain FVIII at 80%–100% levels for 4–5 days or longer.
Monitor vWf:R:Co and FVIII as guide to therapy.

In hemophilia B, when the dose of factor IX for replacement therapy is calculated as described above and given as purified factor IX, the plasma factor IX level rises to only half of that expected from the units of factor IX listed on the bottle. This may reflect binding of infused factor IX to vascular endothelium.

An antifibrinolytic (-aminocaproic acid 2.5 to 4 g po qid for 1 week or tranexamic acid 1.0 to 1.5 g po tid or qid for 1 week) should be given to prevent late bleeding after dental extraction or other causes of oropharyngeal mucosal trauma (e.g., tongue laceration).

effective, this approach is time-consuming and expensive. As an alternative, plasmapheresis can be used to decrease the amount of inhibitors in the blood. The third option is to give either prothrombin complex concentrates, porcine factor VIII or activated recombinant factor VII in an attempt to bypass the need for factor VIII (23,24). Prothrombin complex concentrates are difficult to monitor, are not as effective as factor VIII and can lead to acute myocardial infarction when used in repetitive high doses. Porcine factor VIII is most successful in those patients with no demonstrated cross-reactivity on Bethesda assays. Activated recombinant factor VII works well in many patients but there is no effective way to monitor its activity (24).

Suppression of antibody production by reduction of active B-cell populations holds some promise. At the Haemophilia Centre, Great Ormond Street Children's Hospital in London, Mathias et al. (25) are treating two children who have failed conventional therapy with rituximab (Genentech, San Francisco, Calif.), an anti-CD20 monoclonal antibody. The child with hemophilia B showed no clinical improvement while the other child with hemophilia A showed a good clinical response with a negative inhibitor assay after 11 months. Stasi et al. (26) have reported good results with a small series of ten patients with acquired hemophilia.

The aim of treatment in acquired hemophilia is to restore normal factor VIII levels in circulation using DDAVP, massive

TABLE 28.3
HEMOPHILIA, A TREATMENT EXAMPLE

70 kg Male with hemophilia A
Factor VIII level 0%
Goal is to raise factor VIII levels to 100%.

General approach to raising factor VIII levels in patient with hemophilia A

1. Formula: 100 (%) × 70 (Kg) ÷ 2 = 3,500 units of factor VIII,
2. Measure circulating factor VIII levels and adjust dosage accordingly.
3. Administer second dose between 8–12 hours later.
4. Continue dosage schedule based on measured factor VIII for 7–10 days.

doses of factor VIII, plasmapheresis, and factor VIII infusions while simultaneously treating the immune disorder. Antifactor VIII antibodies (factor VIII inhibitors) develop in 10% to 15% of severely affected hemophiliacs, usually in response to prior factor VIII infusion (22). Most of these patients have extremely low factor VIII levels. Their management is complicated, and patients with hemophilia A should be screened for factor VIII inhibitors before surgery so that appropriate treatment can be used (27). Factor VIII inhibitors occasionally occur in nonhemophiliac patients and can cause a clinical bleeding diathesis with prolonged PTT and decreased factor VIII levels clinically similar to classic hemophilia (28). Factor VIII levels are also decreased in patients with von Willebrand disease because vWF acts as a carrier molecule for factor VIII. Corticosteroids and cyclophosphamide are currently the most widely used treatments for the immune disease (29).

Recombinant factor VIIa is effective as a factor VIII or IX bypassing agent and is relatively safe for the management of bleeding and surgical procedures in patients with factor VIII or IX inhibitors (congenital or acquired hemophilia). It is one of several options in the overall treatment strategy for patients with these difficult conditions. The high cost of this drug may be a limiting factor (30).

Due to the high cost of therapy and limited availability of transfusable coagulation factors there is constant research in the development of alternative products, including gene therapy. The goal of hemophilia gene therapy is to obtain long-term therapeutic levels of factors VIII and IX without stimulating an immune response against the transgene product or vector. Viral vectors are generally far more efficient in achieving this and some have been associated with inflammatory reactions and increased risk (31).

Recently, there has been renewed interest in recombinant technology. At the Indiana Hemophilia and Thrombosis Center, the safety and efficacy of recombinant factor IX was examined. Shapiro et al. (32) found response to rFIX was excellent or good in 94% of patients with previously untreated, moderate to severe hemophilia B. Effective hemostasis termed excellent was achieved in 91% receiving prophylactic rFIX. The only side effect seen was five patients had allergic-type manifestations, and two patients (3%) developed FIX inhibitors. There were no associated thrombotic events or viral transmission.

Factors V, VII, X, XI, XII, and XIII Deficiencies

Hereditary deficiencies of factor V (parahemophilia), factor VII, factor X (Stuart-Prower factor), and factor XI occur, but all are extremely rare. Most are inherited as autosomal recessives, and a great deal of heterogeneity exists within each disorder. Factor V has both procoagulant and anticoagulant properties. Activated factor V stimulates the formation of thrombin, whereas anticoagulant factor V acts as a cofactor for aPC in the degradation of factor VIII/VIIIa, thereby reducing thrombin formation.

An inherited, autosomal recessive deficiency of factor V proaccelerin (or accelerator globulin or labile factor) leads to a rare hemorrhagic tendency known as Owren disease or parahemophilia. It varies greatly in severity from bruising to lethal hemorrhage (33–35). Lak, et al. (36) identified epistaxis and excessive bleeding after surgery as the most common symptoms in 35 Iranian patients with an inherited deficiency of factor V, with plasma levels of 1% to 10%. More severe symptoms, such as gastrointestinal and central nervous system bleeding, were rare. The severity of bleeding symptoms was only partially related to the degree of factor V deficiency in plasma (36). Acquired inhibitors of factor V are rare causes of clinical bleeding, whose severity ranges from mild to life-threatening.

Optimal treatment of patients with factor V inhibitors is uncertain. Fu et al. (37) were successful using a combination of factor replacement, chemotherapy, and plasmapheresis in a patient with spontaneous, life-threatening intracranial bleeding caused by a factor V inhibitor. The patient deteriorated after initial treatment with fresh frozen plasma and platelet transfusions. He was subsequently treated with a combination of plasma exchange and chemotherapy, which led to complete recovery. The experience by Fu et al. (37) shows that combinations of therapy may be needed in patients with serious hemorrhage caused by factor V deficiency or inhibitors.

Only 126 cases of FV inhibitors have been reported in the world's literature. Eighty-seven have been reported in the last decade, of which two thirds are due to an exposure to bovine thrombin. Such exposure can happen after intraoperative exposure to topical thrombin. The resulting antibody-mediated depletion of factor V can cause a severe and

refractory coagulopathy (38). According to Streiff (39), bovine-thrombin associated FV antibodies develop in 40% to 66% of cardiac surgery patients and in 20% of neurosurgery patients. Thirty-three percent of reported patients developed bleeding complications. Inhibitors persisted on average 2.3 months. Standard coagulation assays do not reliably predict clinical manifestations. Multimodality therapy, including immunosuppression, is useful for treatment of symptomatic patients.

Factor VII Deficiency

Factor VII is a vitamin K dependent glycoprotein essential to the extrinsic pathway of coagulation. Deficiencies may be inherited as an autosomal recessive characteristic or acquired in association with vitamin K deficiency, sepsis, autoantibodies, and inhibitors (40,41)

As of 2001, there were 238 individuals described in the world literature with mutations in their factor VII genes (FVII mutation database; europium.csc. mrc.ac.uk) (42). Complete absence of FVII activity in plasma is usually incompatible with life, and individuals die shortly after birth due to severe hemorrhage (43).

Treatment consists of administration of fresh frozen plasma, prothrombin complex concentrates, or factor VII concentrates. Recombinant activated factor VII (rFVIIa) has been used successfully in some patients. Because of the short half-life of factor VIIa, repeated doses have to be administered, and continuous infusion may be even better (44).

The predisposition to bleeding is variable and to some extent depends on the amount of plasma factor VII activity, although this correlation is poor. In congenital factor VII deficiency, the clinical picture is related to the levels of factor VII coagulant activity. Individuals who are homozygous for the mutation who have complete absence of factor VII activity in plasma usually die shortly after birth because of severe hemorrhage. Menorrhagia and metrorrhagia in females and mucosal bleeding and hemarthrosis in both sexes are the most frequent manifestations. Severe bleeding, including hemarthroses, may occur when plasma factor VII levels are below 1%.

The correlation between clinical symptoms and factor VII activity levels in plasma is poor (43). Patients may have prolonged PTs, but the final diagnosis is established by quantitative factor VII assays. This defect prolongs PT, reduces activity of factor VII, and does not affect aPTT. Symptomatic patients have prolonged prothrombin times, but the final diagnosis is established by quantitative factor VII assays. Patients with true deficiencies will have low factor VII activity and low factor VII antigen cross-reacting material (CRM) levels. Others have normal antigen levels but low activity (CRM+) or reduced antigen levels (CRMR).

Three immunological variants of factor VII deficiency exist: VII-, VIIR, and VII+. Conversely, there are two genetic variants: one characterized by no discrepancy between VII: C and VII: Ag (found in the heterozygotes of VII- and VIIR variants) and the other, in which a discrepancy between VII: C and VII: Ag is found (heterozygotes from VII+ kindreds). Other patients may have normal antigen levels but low activity (CRM+) or only reduced antigen levels (CRMR) (45).

Treatment consists of factor replacement with fresh frozen plasma, prothrombin complex concentrates, or factor VII concentrates. Recombinant activated factor VII is a useful alternative. Hunault and Bauer (43) have reported on several patients who have been successfully treated. Because of the short half-life of factor VIIa, repeated doses must be administered.

Combined deficiency of coagulation factor V and factor VIII is an autosomal recessive disorder that has been observed in a number of populations around the world. However, this disease appears to be most common in the Mediterranean basin, particularly in Jews of Sephardic and Middle Eastern origin living in Israel (46).

Factor X Deficiency

Factor X deficiency is a blood coagulation disorder usually inherited as an autosomal recessive trait, though it can be acquired. This deficiency is characterized by defective activity in both the intrinsic and extrinsic pathways, impaired thromboplastin time, and impaired prothrombin consumption. Factor X circulates as a serine protease that is activated at the point of convergence of the intrinsic and extrinsic coagulation pathways. Activated factor Xa is involved in macromolecular complex formation with its cofactor factor Va, a phospholipid surface, and calcium to convert prothrombin into thrombin. The gene encoding factor X shares a number of structural and organizational features in common with the other vitamin K–dependent coagulation proteins, suggesting that they have evolved from a common ancestral gene (47). Factor X deficiency may be acquired in patients with light chain-related amyloidosis. This acquired disorder appears to be secondary to adsorption of factor X to the amyloid fibrils (48). Mumford et al. (49) reviewed 337 cases of patients who had amyloidosis with factor X deficiency. Modest deficiency of factor X was often associated with severe bleeding. In many cases, clinical bleeding could not be accounted for by deficiency of factor X alone, leading the authors to believe that coexistent hemostatic defects probably contributed to the bleeding. Testing with Russell's viper venom may demonstrate an immunoglobulin G inhibitor that selectively inhibits factor X activation (50).

Treatment of acquired factor X deficiency has met with mixed results. Boggio and Green (51) have reported that

control of bleeding with plasma or prothrombin complex concentrates is not completely successful. Smith and colleagues had similar problems in two patients, which led them to resort to daily therapeutic plasma exchange with concomitant administration of intravenous immunoglobulin and steroids. This therapy produced a rapid increase in factor X levels, which controlled the bleeding, followed by gradual recovery of normal factor X levels and correction of coagulation times. Splenectomy eliminates the acquired factor X deficiency in amyloidosis, but control of operative bleeding may require recombinant factor VII.

Factor XI Deficiency

Factor XI deficiency is a congenital deficiency of blood coagulation factor XI (known as plasma thromboplastin antecedent (PTA) or antihemophilic factor C) resulting in a systemic blood-clotting defect called hemophilia C or Rosenthal syndrome, which may resemble classical hemophilia. Factor XI is a key component of the intrinsic pathway of blood coagulation in vitro, but its exact role in vivo is uncertain. Factor XI is activated by thrombin and may participate in clot formation once coagulation has been initiated by other mechanisms. The risk of bleeding in factor XI deficiency depends on the severity of the deficiency in certain situations and on the location of the bleeding site in others. Additional coexisting abnormalities of hemostasis, such as von Willebrand disease, may also be responsible for variation in clinical presentation, particularly in individuals with mild factor XI deficiency (52).

Approximately 40% to 50% of all persons lacking factor XI are of Ashkenazi Jewish extraction (53). Factor XI deficiency is most notable for its variable clinical phenotype, with a total of 39 different FXI mutations identified. O'Connell has reviewed the correlations between these mutations and therapy with antifibrinolytic drugs and recombinant factor VIIa (54). Factor XI deficiency may be suspected in patients evaluated for hemorrhage, an unexplained, prolonged aPTT, or through family or other genetic studies. Women with factor XI deficiency are prone to menorrhagia and to bleeding complications after childbirth (55). Individuals with factor XI deficiency need careful planning for elective surgery and dental extractions. Fresh frozen plasma, fibrin glue, antifibrinolytic drugs, desmopressin, and factor XI concentrates have all been used successfully. Factor XI concentrate is usually reserved for younger patients with severe deficiency because its use in older patients has been associated with thrombotic phenomena.

Factor XII Deficiency

Hageman factor (factor XII) deficiency is defined as an absence or reduced level of blood coagulation factor XII (Hageman factor). Factor XII initiates the intrinsic coagulation cascade and is linked to the fibrinolytic, kallikrein–kinin, and complement systems (56). Factor XII deficiency normally occurs in the absence of patient or family history of hemorrhagic disorders and is marked by prolonged clotting time. Patients deficient in Hageman factor are asymptomatic and generally are identified on screening PTT. The disorder may be suspected in a patient with a prolonged activated partial thromboplastin time (APTT), PT, normal bleeding time, and no clinical history of bleeding. Once suspected, the deficiency can be confirmed by normalization of PTT with plasma component therapy and by factor assay. No treatment is indicated, as abnormal bleeding does not occur after surgery. Decreased factor XII levels prolong the PTT, but even complete absence of factor XII does not cause abnormal bleeding.

Halbmeyer et al. (57) have estimated the prevalence of severe and mild FXII deficiency in the normal population to be 1.5% to 3.0%. This group has identified an association between factor XII deficiency and coronary artery disease. Measurements of plasma factor XII activity, fibrinogen, and lipoprotein(a) in 426 consecutive patients with coronary heart disease awaiting cardiac surgery found 44 (10.3%) who were moderately deficient in factor XII (factor XII activity 17% to 50%, antigen 15% to 57%). The prevalence of factor XII deficiency was significantly higher ($p < 0.0001$) among patients with coronary heart disease than among similarly evaluated 300 healthy blood donors (2.3%) (58).

Hageman factor is also a component of the intrinsic system for the conversion of plasminogen to plasmin, which causes clot lysis. Whether deficiency of factor XII predisposes to thrombosis is uncertain. The index patient (Hageman) died of pulmonary embolism after a pelvic fracture, and thrombotic complications have been reported in other patients with this deficiency. Prekallikrein (Fletcher factor) deficiency and deficiency in HMWK produce clinical syndromes similar to Hageman factor deficiency. The PTT is prolonged, but abnormal bleeding does not occur. Prekallikrein and HMWK are also components of the intrinsic plasminogen activation system.

Factor XII deficiency has clinical significance when attempts are made to heparinize individuals who have this deficiency. Routine coagulation tests used during cardiopulmonary bypass (CPB) are abnormal in factor-XII-deficient patients and are useless for monitoring anticoagulation in these patients. Alternative monitoring systems such as the chromogenic heparin assay, the citrated thrombin time, and the recalcified thrombin time must be used (59).

Factor XIII Deficiency

Factor XIII deficiency is defined as a decrease or absence of factor XIII or fibrin stabilizing factor (FSF) that prevents

blood clot formation and results in a clinical hemorrhagic diathesis. Factor XIII is an enzyme found in plasma, platelets and monocytes. In plasma, XIII has two subunits: the "a" subunit, which is the active enzyme, and the "b" subunit, which is a carrier protein (36). Activated factor XIII stimulates cross-linkage of fibrin as a means of stabilizing clot.

Congenital factor XIII deficiency is a severe autosomal recessive bleeding disorder associated with a characteristic pattern of neonatal hemorrhage and a life-long bleeding diathesis. Untreated patients have a high mortality. Prolonged and recurrent bleeding can follow even relatively minor trauma. Intracranial hemorrhage is a frequent complication (60). The disorder affects both sexes and bleeding may occur during pregnancy. Acquired factor XIII deficiency has been described in Henoch-Schonlein purpura, various forms of colitis, erosive gastritis, and some forms of leukemia. Inhibitors to factor XIII are rare (61). Treatment of factor XIII deficiency requires life long prophylactic therapy with at least monthly infusions of factor XIII concentrate, including during pregnancy.

Von Willebrand's Disease

Von Willebrand's disease (vWD) is much more common than once thought with estimates reaching up to 1% to 2% of the total population being affected. Much confusion has been associated with this disease because as many as 20 different forms have been described. In 1993, at the 39th Annual Meeting of the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis, a new classification system was developed (62). The disease was divided into three major types with Type Two having four sub-types. Type One, found in 80% of cases, includes all the partial quantitative defects of von Willebrand factor (vWF). Type Two (20% of cases) reflects qualitative defects in vWF with Two A representing those patients with decreased platelet vWF interaction and a lack of high molecular weight multimers of vWF. Type Two B is characterized by increased affinity for binding of vWF to platelet Glycoprotein Ib. Other, rare Type Two variants are described in Table 28.4. Type Three describes a type with virtually no vWF at all.

The diagnosis of vWD is sometimes difficult because the bleeding time is not always prolonged in milder cases. The first time any abnormal bleeding is noted may be during the initial surgery. At that time, vWF levels may be falsely elevated because it is also an acute phase protein. It is estimated that nearly 70% to 80% of patients with vWD have Type One disease. Type Two accounts for approximately 20% of all cases, with 15% being Two A and 5% Two B; Type Three accounts for the rest.

Many tests are available for the diagnosis and classification of vWD (63). It is important to use these to classify the type of vWD because treatment varies. DDAVP is the treatment of choice for Type One patients, who have low levels of normal vWF (64). DDAVP given either intravenously or via nasal spray in a dose of 0.3 grams per kilogram body weight should raise vWF threefold to fivefold. The drug releases vWF from storage sites, which binds to factor VIII thereby increasing its activity. Checking the vWF ristocetin cofactor activity, not the bleeding time, tests the effectiveness of the dose. Subsequent doses can be given, but appear to be less effective. Platelet count monitoring is essential when using DDAVP to recognize and avoid drug-induced thrombocytopenia, especially in patients with Type Two B disease.

Therapy for DDAVP failures and qualitative defects of vWF consists of infusion of either fresh frozen plasma or plasma-derived factor VIII formulas that still contain von Willebrand's factor. Recombinant factor VIII and highly purified preparations are of little help in treatment. The goal in treatment of surgical patients should be to keep factor VIII and ristocetin cofactor vWF levels greater than 50%. Major surgery typically requires therapy for 7 to 10 days.

TABLE 28.4
VARIANTS OF VON WILLEBRAND'S DISEASE BY TYPE

Test	1	2A	2B	2N	2M	3	Pt-vWD
vWF antigen	↓	↓	↓	↓	↓	None	↓
Factor VIII	↓	Normal	Normal	↓	Normal	None	Normal
Ristocetin cofactor	↓	↓↓↓	↓	↓↓	↓↓↓	None	↓
RIPA	↓	↓↓	Normal	Normal	↓	None	Normal
RIPA-LD	Absent	Absent	↑	↑	Absent	None	Absent
% multimers present on electrophoresis	70–80	10–12	3–5	1–2	1–2	1–3	0–1

RIPA, ristocetin-induced platelet aggregation; RIPA-LD, low dose ristocetin-induced platelet aggregation; Pt-vWD, platelet type von Willebrand disease.

The antifibrinolytic amino acids episilon amino caproic acid (EACA) and tranexamic acid are important adjuncts in treating vWD, because rapid clot lysis may quickly overcome factor therapy and initiate rebleeding (65). These drugs bind to plasminogen and plasmin, preventing fibrinolysis. They can be given intravenously, by mouth, or topically. Doses are 50 to 75 mg per kg four times a day for EACA and 25 mg per kg three times a day for tranexamic acid.

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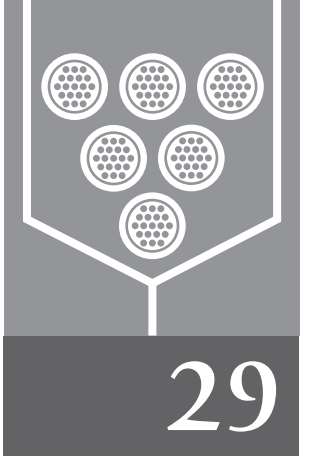

29

Perioperative Implications of Anticoagulant and Antiplatelet Therapy

Jeffrey A. Green

Anticoagulant and antiplatelet medications have important implications for the perioperative medical team. The effect of these drugs on surgical patients is important to consider for two of their uses; acute postoperative venous thromboembolism (VTE) prophylaxis, and chronic anticoagulant or antiplatelet therapy. The appropriate selection of drug and management of patients undergoing surgical procedures is paramount to successful surgery without VTE or bleeding complications and transfusion. Furthermore, the use of central neuraxial regional anesthesia must be used with caution in this setting. These areas are discussed in this chapter.

The recognition and awareness that surgery is associated with a 20-fold to100-fold increased risk of VTE has dramatically expanded the use of anticoagulant medications for perioperative prophylaxis for acute VTE (1,2). The development of low molecular weight heparin (LMWH) compounds with their wide therapeutic index and enhanced safety profile has improved the prevention VTE in the postoperative period. The perioperative physician must have a thorough knowledge and understanding of the mechanisms of action, risks and benefits of each medication, and their approved indications.

As indications have broadened, the use of chronic anticoagulation and antiplatelet therapy is increasing dramatically in clinical practice. In addition, a new class of agents, known as direct thrombin inhibitors, has the potential to revolutionize the delivery and monitoring of chronic anticoagulation. Furthermore, the expanded role of antiplatelet agents, some with long half-lives, have had a dramatic reduction in thrombotic events. However, the increased prevalence of these drugs with associated risks of perioperative bleeding has made the management of surgical patients more complex.

RISK OF VTE AND SCOPE OF THE PROBLEM

VTE is exceedingly common. The incidence of perioperative symptomatic VTE is estimated to be 0.8% to 7.5% depending on the procedure (2). For example, in total hip arthroplasty, pulmonary embolus (PE) may account for as much as 10% of all mortality associated with the procedure (3). The overall risk of symptomatic VTE is directly related to type of surgery, presence of other risk factors, duration and extent of postoperative immobilization, and the use or nonuse of specific thromboprophylactic measures. In general, the risk of VTE can be divided into four categories, as stratified by the American College of Chest Physicians (ACCP) (Table 29.1) (4).

Along with symptomatic VTE, there is a substantial incidence of subclinical and asymptomatic deep venous thrombosis (DVT). This is important because most clinical trials examine the incidence of asymptomatic DVT by

TABLE 29.1
CATEGORIES OF RISK AND INCIDENCE OF VTE

Level of Risk	Age	Type of Surgery	Additional Risk Factors	Incidence DVT%	Incidence PE%
Low	<40	Minor	None	0.4	<0.5
Moderate				2–4	1–2
A	Any	Minor	Present		
B	<40	Major	None		
C	40–60	Nonmajor	None		
High				4–8	2–4
A	>60	Nonmajor	Present or none		
B	>40	Major	None		
C	>40	Major	Present		
Highest				10–20	4–10
A	Any	Hip or knee, major trauma, spinal cord injury			
B	>40	Major	Prior VTE, cancer, hypercoagulable state		

ultrasound or contrast venography. The percentage of patients that develop clinically significant symptoms or PE related to asymptomatic DVT is unknown. The pathophysiology of VTE, therefore, can be considered as an iceberg, where symptomatic VTE represents only the tip of an underlying larger clinical problem (Figure 29.1).

There are specific additional risk factors identified which contribute to risk (2). They can be classified into standard, hereditary, or acquired (Table 29.2).

Factor V Leiden (FVL) is now known as the most common inherited cause of thrombophilia (5). It is present in 5% of the Caucasian population. The literature examining FVL as an additive risk in the perioperative period is controversial. Most studies in noncardiac surgery do not identify FVL as an additional risk; this may be due to the large risk of VTE alone and current postoperative management strategies may overwhelm the relative small effect of FVL. The exception to this may be vascular surgery where FVL may play a role in increased arterial thrombosis (6,7). In cardiac surgery, FVL patients are likely to bleed less (equivalent to antifibrinolytic therapy), however there is evidence that there may also be increased early CABG graft

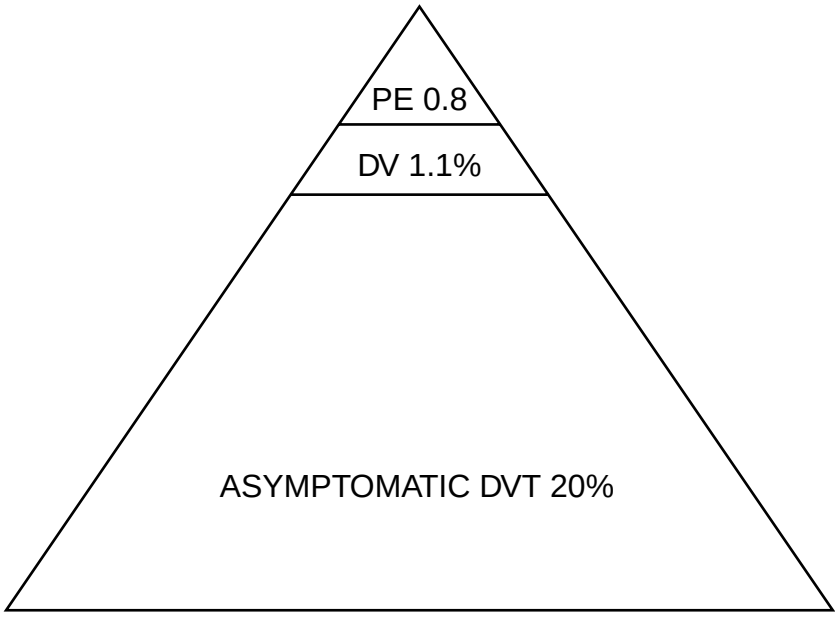

Figure 29.1 Symptomatic versus asymptomatic VTE.

TABLE 29.2
RISK FACTORS FOR VTE

Risk Factor	Effect
Standard	
Age	Exponential increase in risk after age 40
Ethnicity	African American>Caucasian>Latino>>Asian (threefold lower)
Type of surgical procedure	Up to sixfold higher with total joint, craniotomy. Other major vascular, bowel, radical cystectomy, gastric bypass, kidney transplant all with increased risk.
Trauma	Especially pelvic, femur, lower leg fracture
Previous VTE	Threefold to fourfold higher, especially within last 6 months
Venous stasis (CHF, COPD)	Increased
Female gender (pregnancy, estrogen use)	Increased
Stroke, prolonged immobilization, bedrest	Early mobilization reduces risk
Obesity (Body Mass Index [BMI] >30)	Increased with increasing BMI (? Due to underdosing or sequential compression device (SCD) failure)
Hereditary	
Thrombophilic disorders (should be investigated in any patient presenting without other obvious predisposing factor or repeated thrombosis)	FV Leiden mutation, lupus anticoagulant or anticardiolipin fivefold to 10-fold increased, ATIII mutation, prothrombin gene mutation twofold to threefold increased, MTHFR mutation, protein C,S deficiency, Increased FVIII, IX, X
Heparin	
■ Heparin induced thrombocytopenia (HIT)	
■ Antithrombin III deficiency	
Acquired chronic	
Malignancy	1.7–2 fold higher, especially advanced stage or adenocarcinoma
Antiphospholipid syndrome, hyperlipidemia, hyperhomocysteinemia, nephrotic syndrome, myeloproliferative disorders, endotoxemia	Increased
Acquired transient	
Warfarin	Increased due to inhibition of protein C
Heparin	
■ HIT/TS	20-fold–40-fold increased risk
■ AT deficiency	4.2–5.3 fold increased risk

occlusions. There may be an interaction with antifibrinolytic drugs, especially lysine analogs (5).

Patients with Prior Postoperative VTE

Patients with a history of VTE presenting for a surgical procedure represent a specific high risk group. Many clinical trials using low molecular weight heparins (LMWHs) to prevent postoperative thrombosis have specifically excluded patients with a previous history of thrombosis or pulmonary embolism, making it particularly difficult to estimate the relative risk increase.

In general, elective surgery should be avoided in the first month after VTE. If not possible, it is recommended to anticoagulate with heparin preceding and following surgery. If heparin is not possible, a perioperative vena caval filter should be considered (1).

CURRENT INDICATIONS FOR PROPHYLACTIC ANTICOAGULANT AND ANTITHROMBOTIC AGENTS

Guidelines for the safe administration of anticoagulant and antithrombotic agents continue to evolve as the evidence for the degree and duration of anticoagulation as well as advances in drug development occur. Recommendations from the ACCP, last published in 2004, (8) are based on

prospective randomized trials. However, the primary outcomes of these trials are the detection of asymptomatic DVT measured by ultrasound or venography, not fatal PE or symptomatic DVT. In order to complete studies with symptomatic VTE as an endpoint would require a large number of patients and increased expense. Since first reported in 1986, the ACCP recommendations have consistently and progressively supported higher intensity and longer duration anticoagulation. The data from the 7th Consensus Conference on Antithrombotic and Thrombolytic Therapy (8) are included below.

Nonpharmacologic Methods

There is a significant amount of literature to support nonpharmacologic methods for VTE prophylaxis. The data support the conclusion that nonpharmacologic prophylaxis is widely used and extremely safe. These methods include early ambulation, direct compression devices, elastic stockings, and invasive filters. In particular, in the orthopedic surgery population, early ambulation can be as effective as pharmacologic therapy (9,10). Based on the ACCP consensus statements, early mobilization is the method of choice for VTE prophylaxis for minor general surgery, spine, vascular, and arthroscopy in patients without additional risk factors (8).

The simplest device method is the use of elastic stockings, which are also known as compression stockings, or TED hose. Elastic stockings are effective if they fit properly, but should not be used as a solo therapy in high risk patients (11–13). Sequential compression devices, which are mechanical stockings that intermittently compress the lower extremities using air or other means, can be a primary method in select populations such as patients with gynecological malignancy, but are additive when used with pharmacologic methods. Although invasive, the IVC filter is safe and effective at reducing PE, but increases the frequency of recurrent DVTs (14–16).

Warfarin

Warfarin inhibits vitamin K epoxide reductase and vitamin K reductase, blocking the conversion of vitamin K epoxide to vitamin K. Vitamin K depletion results in defective factors II, VII, IX, and X. Warfarin is metabolized in the liver and excreted in urine and stool. It is reversible by vitamin K, FFP, or prothrombin complex concentrate (1).

Warfarin has enjoyed long use in the prevention and treatment of venous thrombosis and pulmonary emboli, as well as the prevention of stroke in patients with rheumatic valve disease and thrombogenic prosthetic heart valves (17). Other major indications include atrial fibrillation, ventricular mural thrombi after myocardial infarction, and thrombophilia (18).

Despite its indications, warfarin is greatly underutilized for stroke prevention. This is mostly due to physician reluctance to prescribe, in part because they are not familiar with techniques for administering the drug safely and fear that the drug will cause bleeding. Patients treated with warfarin do require close monitoring to avoid bleeding, but it has been shown that the drug prevents 20 strokes for every bleeding episode that it causes (17).

The recognition that lower intensity oral anticoagulation is effective in preventing a number of thrombotic events while not causing an intolerable increase in bleeding risk has enhanced the use of long-term oral anticoagulation. However, warfarin requires more intensive monitoring due to its potential for bleeding (19). It is most useful in extended prophylaxis in high risk patients, but carries a higher incidence of asymtomatic DVT due to delayed onset of action. Furthermore, warfarin carries the risk of paradoxical hypercoagulability during the first 36 hours of therapy. Warfarin also requires significant dose adjustment in the elderly (20).

Although many of the newer agents have replaced warfarin in some clinical areas due to its narrow therapeutic window, there is not yet another oral anticoagulant to supplant its use. There is data to support its use for VTE prophylaxis in orthopedic surgery that demonstrate that it is comparable to enoxaparin (21–25). Warfarin is the most cost-effective prophylactic strategy (26).

The typical perioperative dosing is a two-stage approach with a low dose targeting an INR 1.5 for 10 to 14 days preoperatively then increasing to a target INR of 2.5 postoperatively (27). In patients for total hip or knee replacement and hip fracture, the ACCP has more recently recommended starting warfarin the night before or immediately after surgery, adjusted to a target INR of 2 to 3, as an alternative strategy to LMWH or fondaparinux sodium (8).

Unfractioned Heparin (UHF)

Heparin is the most commonly used anticoagulant. It is clearly effective in reducing risks of intravascular thrombosis. Full anticoagulant doses can lead to bleeding complications and hematoma formation. In its unfractionated form, it is a negatively charged, water-soluble mucopolysaccharide acid with molecular weight of 15,000 daltons. Heparin forms a complex with antithrombin III (ATIII), which binds to thrombin and to a lesser extent factors IX, XI, and XII blocking their actions. Heparin impedes thrombin generation by inhibiting factor Xa and blocking positive feedback loops to factors V and VIII. Heparin has a half-life of 60 minutes and is cleared by the kidney

with endothelial uptake. It is completely reversible by protamine (1).

Given by subcutaneous injection to low or moderate risk patients, the efficacy of UFH is equivalent to LMWH with a moderate increased risk of bleeding (28–30). It has been shown to be less effective than LMWH in high risk patients (28,31).

Current indications are for patients with additional risk factors undergoing major general or gynecologic surgery, and high risk urologic surgery when dosed at 5,000 units SC every 8 hours, starting 2 hours before surgery (8,32,33). Heparin is also indicated in patients with additional risk factors undergoing minor general surgery, vascular, or spine surgery when dosed at 5,000 units subcutaneous every 8 hours, starting 2 hours before surgery (8). Lastly, UFH is indicated in major general or gynecologic surgery, when there are no additional risk factors, at a dose of 5,000 units SC every 12 hours, starting 2 hours before surgery (8). Even in adjusted or low dose regimens, is no longer recommended as the only method of prophylaxis in hip or knee replacements, but is recommended in hip fracture surgery (8).

The safety risks include excess bleeding and the development of heparin-induced thrombocytopenia (HIT), which can be life threatening. The incidence of bleeding in a study of total hip arthroplasty procedures was 2.6% with heparin, 1.8% with LMWH, and 0.3% with placebo (23). In another study of general surgery patients, there was increased bleeding compared to LMWH (28,31).

Low Molecular Weight Heparins

The development of various LMWH compounds has had a dramatically positive impact on postoperative surgical care. These are fragments of unfractionated heparin with a weight averaging about 5,000 daltons. LMWH binds to ATIII but with far less antifactor IIa activity (1). Currently there are two low molecular weight heparin formulations available in North America for treatment, enoxaparin (Lovenox), and dalteparin (Fragmin) (Table 29.3).

LMWHs have advantages over other methods of preventing postoperative VTE (34–37). Unlike warfarin, LMWHs do not require adjustment based on laboratory monitoring. This eliminates the need for daily prothrombin times (PT), International Normalized Ratios (INR), or activated partial thromboplastin times (aPTTs) in the postoperative period. The route of administration with is subcutaneous. The compounds have a sustained release for the subcutaneous injection site and thus permit twice daily or sometimes once daily subcutaneous dosing due to longer biologic half-life and more predictable bioavailability compared to UFH (Table 29.4).

TABLE 29.3
RECOMMENDED DOSING FOR COMMON SURGICAL PROCEDURES[a]

Total Hip or Knee Replacement Thrombophylaxis	Dose
LMWH	
■ Ardeparin (Normiflow)	50U/kg SC q12 started 12–24 hours after surgery
■ Dalteparin (Fragmin)	5,000U SC qd started 12 hours before surgery, or 2,500U SC given 7 hours after surgery, then 5,000 U SC qd
■ Danaparoid (Orgaran)	750U SC q12 started 2 hours before surgery
■ Enoxaparin (Lovenox)	30 mg SC q12 started 12–24 hours after surgery, or 40 mg SC qd started 10–12 hours before surgery
■ Tinzaparin (Innohep)	75U/kg SC qd started 10–12 hours before surgery
Fodaparinux (Arixtra)	2.5 mg SC qd started 6 hours after surgery
Warfarin	5 mg PO started the night before or immediately after surgery and adjusted to INR 2.0–3.0
General surgery thromboprophylaxis	**Dose**
Unfractionated heparin	5,000 U SC q8–12 started 2 hours before surgery
LMWH	
■ Dalteparin	2,500U SC qd started 1–2 hours before surgery
■ Enoxaparin	40 mg SC qd started 2 hours before surgery

[a] Adapted from Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: Defining the risks. (The second ASRA consensus conference on neuraxial anesthesia and anticoagulation). *Reg Anesth Pain Med.* 2003;28(3):172–197.

TABLE 29.4
COMPARATIVE PHARMACOKINETIC PROFILES OF UFH AND LMWH[i]

Drug	UFH	Ardeparin	Dalteparin	Danaparoid	Enoxaparin	Tinzaparin
Mean molecular weight (Daltons)	15,000	6,000	5,000	5,500	4,500	5,500-7,500
Anti-factor Xa to anti-factor IIa activity ratio	1:1	2:1	3:1	>22:1	3:1-14:1	2.8:1
Mean bioavailability (route)	22-40% (IV)	92% (SC)	87% (SC)	100% (SC)	92% (SC)	87% (SC)
Half-life (hours)	<1.0	1-3	3-5	24.5	4.5	3-4
Peak anti-factor Xa activity (hours)	2-4	2-3	4	2-5	3-5	4.5

[i]Becker RC, Fintel DJ, Green D. *Antithrombotic Therapy* (2nd Edition). New York: Professional Communications, Inc., 2002.

There appears to be no effect on platelets. LMWHs have decreased sensitivity to circulating heparin inhibitors (1). Unfortunately, the optimal duration of use of the LMWHs after surgery is not known.

The safety and efficacy of LMWHs for VTE prophylaxis has been demonstrated. They are currently indicated in trauma, (38) general and urologic surgery, (23,28,30,31,39) and orthopedics (23,40–42). Several studies have demonstrated their safety with lower bleeding rates than UFH (23,28,30,31,41,42). Originally LMWH were started 6 hours postoperatively due to the perceived risks of intraoperative bleeding (43) but recently data has accumulated suggesting the timing of the dose preoperatively may be more effective (44).

There is little data on the duration of prophylaxis. It has been suggested that there is diminishing returns for extended duration beyond hospitalization in general surgery patients (45–47). However, in orthopedic patients, the recommended duration is a minimum of 10 days of treatment. It is not uncommon for extended prophylaxis, especially in total joint patients up to 35 days (48,49).

Despite the advantages, there still remain risks with LMWH. Although the incidence is lower than with UFH, LMWH can cause HIT. Furthermore, the longer duration of action of LMWH requires advanced planning prior to surgical procedures or regional anesthesia, as will be discussed later.

LMWH is also indicated for the treatment of acute coronary syndromes and treatment of VTE. The approved indications and dosing are presented in Table 29.5.

Pentasaccharide

Fondaparinux sodium (Arixtra) is a low molecular weight pentasaccharide with selective inhibition of factor Xa via antithrombin. In clinical studies, decreased thrombi were

TABLE 29.5
TREATMENT OF ACS OR VTE[a]

Drug	Dose (All SQ)	Indication
Dalteparin (Fragmin)	120IU/kg q12h	Unstable angina, Non-ST elevation MI, prevention of ischemic complications in patients on ASA.
Enoxaparin (Lovenox)	1mg/kg q12h or 1.5mg/kg qd	Prevention of ischemic complications of unstable angina and non-ST elevation MI with ASA, inpatient treatment of DVT/PE with warfarin, outpatient treatment of DVT w/o PE with warfarin
Tinzaparin (Innohep)	175IU/kg qd	Inpatient treatment of acute DVT/PE with warfarin
Fondaparinux (Arixtra)	7.5 mg qd	Treatment of acute DVT/PE with warfarin, dose adjustment required <50 kg or >100 kg

[a]Adapted from L evine MN, Hirsh J, Gent M, et al. Prevention of deep vein thrombosis after elective hip surgery. A randomized trial comparing low molecular weight heparin with standard unfractioned heparin. *Ann Intern Med.* 1991;114(7):545–551.

demonstrated by venogram, but there was no decrease in symptomatic VTE events in total hip arthroplasty or total knee arthroplasty (50–52). There appears to be no known effect on platelets.

Fondaparinux is indicated for the prevention of VTE in hip fracture surgery, hip replacement surgery, knee replacement surgery, and high risk patients undergoing abdominal surgery. Fondaparinux, dosed at 2.5 mg SC at 6 hours postoperatively is more effective (cut VTE by >50%) and as safe as enoxaparin (53,54). Fondaparinux is also indicated for the treatment of VTE at a dose of 7.5 mg SC per day for patients 50 to100 kg until a therapeutic INR is established on warfarin (53). Due to the extended half-life of fondaparinux (approximately 20 hours), both the American Society of Regional Anesthesia and Pain Medicine (ASRA) and ACCP recommend against the use of the drug in the presence of an indwelling catheter for regional anesthesia (34).

Aspirin

Aspirin (ASA) irreversibly inhibits platelet cyclo-oxygenase and prevents synthesis of thromboxane A2, which is involved in secondary platelet aggregation resulting in a fragile clot (1). ASA is widely used as an antithrombotic agent to prevent arterial thrombotic events other than stroke in atrial fibrillation patients. ASA is indicated in patients with stable angina, unstable angina, acute myocardial infarction, transient ischemic attacks, thrombotic stroke, and peripheral vascular disease (54). ASA will reduce the incidence of stroke in patients with chronic atrial fibrillation by approximately one third and is recommended for those patients with atrial fibrillation who cannot take warfarin therapy (55).

Compelling data indicate that ASA is effective in prevention of stroke in patients with transient ischemic attacks, (56–58) prevention of stroke in patients with nonvalvular atrial fibrillation, (59,60) and in the prevention of myocardial infarction (61–63). The relatively low cost and lack of need for therapeutic monitoring have been significant factors leading to the use of aspirin. ASA is not recommended as sole VTE prophylaxis for any procedure, (4) but along with LMWH for hip patients due to a decrease in fatal PE (64).

Clopidogrel (Plavix)

Clopidogrel is an inhibitor of adenine diphosphate-induced platelet aggregation. In combination with ASA, which blocks the thromboxane-mediated pathway, it is recommended as the standard therapy for prevention of coronary artery stent thrombosis (65). Plavix used within 4 days of operation is associated with increased blood loss and reoperation and is an independent risk factor for increased transfusions, increased ICU length of stay (LOS), and increased total LOS (66,67). Hemostasis was normalized after 4 days of discontinuation of clopidogrel and ASA, or when about 50% of the platelet pool was renewed. It is advisable to wait for surgery when possible for patients on clopidogrel. Clopidogrel is not indicated for prophylaxis of VTE.

Direct Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) are a new class of anticoagulant, which inhibit thrombin directly to produce profound anticoagulation. This new mechanism of action allows for different properties of these drugs, including the ability to be used in patients with or at risk for HIT. Several DTIs are available for parental use (lepirudin, bivalirudin, argatroban) but will not be discussed here.

Ximelagatran (Exanta)

Although this medication is not yet available in North America, it merits discussion as the first oral direct thrombin inhibitor in U.S. clinical trials. In the Sportif V trial, 3,922 patients with atrial fibrillation were randomized to ximelegatran or warfarin (68). Ximelegatran was associated with fewer strokes and systemic emboli and statistically significantly less bleeding. The FDA did not approve the drug in September 2004 due to elevations in liver enzymes and potential hepatic toxicity. In another study in total knee arthroplasty patients, ximelegatran had similar safety and efficacy to enoxaparin (69). There is no need to monitor anticoagulant levels with this drug. If it were available it would represent a significant advance compared to warfarin due to the increased patient comfort and convenience (70,71).

Melagatran

The injectable formulation of ximelegatran, melagatran, is indicated for prevention of VTE in hip or knee replacement. Melagatran is not more effective than dalteparin, and must be used in high doses to achieve appreciable decrease in DVTs. It is associated with increased bleeding (72–75).

Desirudin (Iprivask)

Desirudin is a synthetic recombinant hirudin compound indicated for VTE prophylaxis in hip replacement surgery. In one study, given 30 minutes preoperatively, it was more effective than enoxaparin when given 12 hours preoperatively with less DVT and same amount of bleeding complications (76).

Risk of Bleeding

Bleeding is the major complication of anticoagulant and thrombolytic therapy. Bleeding is major if it is intracranial,

intraspinal, intraocular, mediastinal, or retroperitoneal, leads directly to death, or results in hospitalization or transfusion. Risk factors for major bleeding include the intensity of the anticoagulation, increased age, female gender, history of GI bleeding, concomitant ASA use, and length of therapy (19). During warfarin therapy, an INR from 2 to 3 is associated with lower risk, while an INR >4 represents a higher bleeding risk. Hemorrhagic complications during therapeutic coagulation with heparin and LMWH is <3%.

INCREASED USE OF ACUTE AND CHRONIC ANTICOAGULATION AND ANTIPLATELET THERAPY

The use of long-term oral anticoagulation with warfarin is increasing. In fact, the use of warfarin and ASA from 1980 to 1994 increased by 200% (77). This is particularly evident in the prevention of stroke in older patients with chronic atrial fibrillation. An impressive body of data supporting the use of oral anticoagulation to prevent stroke in patients with atrial fibrillation has led to the prescription of warfarin to many older patients who previously would not have been considered for such long-term therapy. Between 5% and 6% of people in their seventies have atrial fibrillation; this can occur in the absence of underlying mitral valve disease or congestive heart failure (78). The risk of stroke in patients with atrial fibrillation is approximately six times higher than in patients without atrial fibrillation (79). Warfarin has been shown in six large collaborative trials to reduce the incidence of stroke by approximately 60% (80). This has prompted the recommendation that all patients over age 65 years who have atrial fibrillation and an associated risk factor, such as prior transient ischemic attack or stroke, hypertension, heart failure, diabetes, clinically evident coronary artery disease, mitral stenosis, prosthetic heart valves, or thyrotoxicosis, should receive long-term oral anticoagulation with warfarin (81). This means that potentially 5% of patients in their seventies will be receiving oral anticoagulation, which will need to be safely discontinued before elective surgery and restarted after surgery. The risks of warfarin are 1.7% for major bleeding, 16.6% for minor beeding, 1.2% for ischemic stroke, and 0.3% for TIA (82).

ASA has been studied as a solo therapy for atrial fibrillation. In several large, randomized trials, it was determined that ASA was effective in decreasing stroke, however it was not nearly as effective as warfarin (83). In another trial evaluating low intensity warfarin anticoagulation (INR 1.2 to 1.5) plus ASA, there was an increased rate of primary events prompting early termination of the trial. When combined with moderate intensity warfarin anticoagulation (INR 1.4 to 2), ASA has been demonstrated to produce less vascular events and less bleeding than warfarin alone (84). Currently, the ACCP recommends ASA therapy alone for patients less than 65 without any other stroke risk factors or for those unwilling or unable to take warfarin (18,39).

Similarly, the use of antiplatelet therapy has dramatically increased during the last decade. There is controversial, yet suggestive, evidence that long-term treatment with clopidogrel in patients with coronary artery disease and/or other vascular disease is beneficial (85–89). Most of the research has focused on the role of clopidogrel after PCI with or without stent. Although long-term data is still accumulating, it is likely that lifelong treatment will provide a greater risk reduction for recurrence of vascular events than the other conventional treatments for atherosclerosis, such as ASA after MI, ACE-inhibitors, or statins (90). This paradigm shift has major implications for the perioperative physician in the management of these patients who are taking long-acting platelet inhibitors.

ANTICOAGULANTS AND SURGICAL BLEEDING

Perioperative management requires weighing the opposing risks of increased surgical bleeding from residual anticoagulation versus potential thrombotic or embolic events from withholding the chronic anticoagulant, due to the increased risk of thromboembolism induced by surgery. An effective and safe plan must be determined prior to surgery. This decision is based in part on the type of operation, type of anticoagulant, patient risk factors, and the indication for anticoagulation (1). Implementing an optimal thromboprophylaxis regimen requires simultaneous assessment of the risks of VTE and the risks of bleeding. After combining these estimates with evidence-based knowledge regarding the efficacy and safety of various thromboprophylaxis modalities, one can make an appropriate treatment recommendation (2).

Coronary Artery Bypass Surgery

Patients undergoing CABG are unique for several reasons. First, this group of patients has advanced coronary atherosclerosis and usually concomitant peripheral vascular and cerebrovascular disease. Second, new vascular conduits will provide an additional nidus for thrombus formation. It would seem logical that this group would greatly benefit from antithrombotic and antiplatelet therapy. CABG requiring cardiopulmonary bypass (CPB) initiates a cascade of

perturbations of the hemostatic system that predispose toward bleeding even without the influence of external anticoagulants. In fact, CPB results in a relative anticoagulated state that persists into the postbypass period. The overall incidence of saphenous vein bypass grafts that thrombose is unknown since routine angiography is not usually performed. Furthermore, the risk of PE after cardiac surgery is relatively small at 0.43 to 1.1% (91). The risks of surgical bleeding and risks of increased transfusion and reoperation are significant and must be weighed against the risks of thrombosis or graft occlusion (92).

In a prospective study, patients receiving 325 mg ASA 12 hours before bypass surgery had increased operative blood loss and receive more packed red blood cells and more blood products than did patients who were not treated with ASA (93). Additional prospective studies have found similar results (94). The dosing and timing of ASA before or after surgery appears to be critical. A retrospective examination of a cohort of patients who received ASA within 1 week of admission for bypass surgery did not find significantly increased homologous blood requirements (95). A case-control study examining 90 patients who underwent reoperation for bleeding after coronary artery concluded that ASA exposure within 7 days before bypass surgery was associated with an increased rate of reoperation for bleeding and increased use of blood products (96). The increased blood loss that is seen with perioperative ASA use must be weighed against improved early graft patency rates (97) and patency rates at 1 year (98,99). Overall, the data reveal improved saphenous vein graft patency with ASA administration of at least 325 mg daily (39). Usually this dose is started perioperatively and continued permanently.

Patients on clopidogrel presenting for cardiac surgery represent a specific high risk group. Due to its high potency and longer half-life, careful planning must be used for these patients.

Multiple studies have demonstrated an increase in adverse events in patients taking clopidogrel prior to CABG, including increased chest tube drainage, increase transfusion, more reoperations, longer intubation times, increased platelet transfusion, and increased mortality (100–103). Furthermore, it appears that clopidogrel and ASA are synergistic, resulting in increased bleeding. The ACCP currently recommends cessation of clopidogrel therapy for >5 days for elective cardiac surgery (19). In emergency situations, there is evidence that aprotinin, a serine protease inhibitor with hemostatic effects, is protective of platelets in the presence of patients on clopidogrel and may be beneficial in these situations (104). The latest ACCP recommendation for the use of clopidogrel in CABG patients is for those postoperative patients who are unable to take ASA (8).

Perioperative Management in Patients on Chronic Oral Anticoagulation

Patients, such as those with thrombogenic heart valves, need relatively high intensity oral anticoagulation and are at significant risk of stroke when that therapy is interrupted. The perioperative management must be individualized balancing the risks of thromboembolism if therapy is interrupted versus the risks of bleeding if such therapy if continued (2). When elective surgery is a necessity, oral anticoagulation is stopped for the shortest possible period of time. In the traditional model, on between the third and fifth day before surgery, the patient is instructed to stop taking the oral anticoagulant. Patients maintained at an INR of 2 to 3 will usually return to an INR of <1.5. For patients with INR maintained >3 or those who require an INR <1.3 for surgery, oral anticoagulation should be stopped sooner. On the second day before surgery, the patient enters the hospital and is placed on full-dose intravenous heparin. This is continued until the morning of surgery when the heparin is stopped 3 to 6 hours before the procedure. After surgery, full dose heparin therapy is reinstituted as soon as possible with concomitant reinstitution of oral anticoagulation. The administration of vitamin k is avoided because its use can make the subsequent use of oral anticoagulation difficult and can prolong the time required to attain a therapeutic level of oral anticoagulation (79,105).

If emergency surgery is necessary, the use of large doses of vitamin k should be avoided if possible. A dose of 3 to 5 mg given subcutaneously should have a maximal effect in correcting PT. The use of fresh frozen plasma immediately before surgery may be necessary. However, because the effects of fresh frozen plasma are dependent on the short half-life of factor VII, the plasma must be given as shortly before surgery as cardiovascular status permits. An adequate dose of fresh frozen plasma is often about one third of the plasma volume or typically 800 to 1,000 mL (3 to 5 units). Recently, there have been multiple case reports of the use of recombinant human factor VIIa (Novoseven) for surgical bleeding in cases of life-threatening coagulopathy (106). There are currently randomized prospective clinical trials underway.

Unfortunately, there are no controlled studies examining the risks of bleeding in patients receiving differing intensities of oral anticoagulation. The amount of blood loss cannot be predicted exactly based on the PT or INR. Physicians can only assume that the more closely the PT or INR is to normal, the less operative blood loss there will be.

A more recent approach to the perioperative management of anticoagulation is to consider options for anticoagulation management based on the risks of bleeding of

the procedure. The three options include (a) continue therapy, (b) discontinue therapy and use prophylaxis, (c) discontinue therapy and heparinize. There is emerging evidence that low risk procedures such as cataract, laparoscopic cholecystectomy, and dermatology procedures can be completed while remaining on warfarin therapy. Other procedures such as dental surgery, endoscopy, and even TURP can be performed under lower intensity anticoagulation with shorter interruptions in anticoagulation. For higher risk procedures, the decision to heparinize or not is based on individual patient risk factors (107). One effective technique is to use LMWH as a bridging therapy during interruptions in anticoagulation (2). This can be done on an outpatient basis and has been demonstrated to be cost effective and safe (108).

Patients taking certain herbal preparations are also at risk for perioperative bleeding. Herbs such as ginko, garlic, and ginseng are known platelet inhibitors (109). Although there is no evidence to support discontinuation of these medications, the medical team should be prepared for their additive effects in high risk patients, especially those on other forms of anticoagulation or antiplatelet therapy.

ANTICOAGULANTS AND SPINAL AND EPIDURAL ANESTHESIA

There is considerable concern about the risk of epidural or spinal anesthesia in patients receiving LMWH and other potent antithrombotic drugs. As LMWHs have become more widely used and the indications for their use broaden, this will remain an issue of major interest.

Using an extensive European database, Wolf (110) reviewed 9,006 patients who received epidural or spinal anesthesia while receiving LMWH. None of these patients experienced any neurological complications due to hemorrhage at the puncture site. Bergqvist (111) performed an extensive review of the literature in this area and concluded that neurological complications after epidural or spinal anesthesia in patients receiving postoperative thromboprophylaxis with LMWH in low doses and low dose UFH are extremely rare. It was concluded that the use of these prophylactic measures is safe in this setting. After their extensive review of the literature from 1906 to 1994 (61 cases), Vandermuelan et al. (112) concluded that the benefits of LMWH use outweigh the risk of local hemorrhage after spinal and epidural anesthesia. They suggested that subcutaneous LMWH should be started 10 to 12 hours before the anesthesia, or at least 1 hour after the spinal or epidural anesthesia is initiated. They further suggested that epidural or spinal catheters should be removed at least 10 to 12 hours after the last dose of LMWH. Unfortunately, given the infrequency of hemorrhage complications after this type of anesthesia, controlled studies to resolve the correct timing of the anesthesia and LMWH administration are not possible due to the large number of patients required.

The ASRA published the results from its Second Consensus Conference on Neuraxial Anesthesia and Anticoagulation in 2003 (34). Of note, although there are case reports of spinal hematoma in the literature, because such an event is so rare, no clinical study to date has had sufficient power to definitively determine patient management. The incidence of epidural hematoma is estimated to be 1:150,000 and for spinal anesthesia 1:220,000 (34). Therefore, regional anesthesia in the anticoagulated patient remains an area where judgment of the responsible anesthesiologist must weigh safe and quality anesthesia care with the benefits of regional anesthesia.

The following recommendations were made by the consensus conference:

Thrombolytic or Fibrinolytic Therapy

Patients on these medications are at risk for serious hemorrhagic events. These drugs are usually used in combination with heparin and antiplatelet medications, which will exacerbate the risk of bleeding. The consensus conference concluded that central neuraxial anesthesia should be used only in extremely unusual situations. Furthermore, if a patient with an indwelling catheter unexpectedly receives these drugs, it may be beneficial to measure the fibrinogen level before the removal of the catheter.

Heparin

There is no contraindication to regional anesthesia for patients on subcutaneous heparin prophylaxis. Heparin should be delayed until after the block if possible. If there is planned therapeutic heparin to be given intraoperatively, for example an IV bolus for peripheral vascular surgery, then neuraxial anesthesia should be avoided only when there is evidence of an existing coagulopathy. It is preferable to delay heparin for greater than 1 hour after needle placement, and catheters should be removed only 2 to 4 hours after stopping heparin. Before restarting heparin, wait to reheparinize for 1 hour, then monitor closely, and consider minimal local anesthetic concentration to allow for appropriate neurologic examination. There is no data to support cancellation of surgery if blood is encountered during needle placement. There is also no data in cardiac surgery where full systemic heparinization is planned. The consensus conference recommends taking precautions when other anticoagulants such as platelet inhibitors are present and supports delaying cardiac surgery for 24 hours after a traumatic needle placement.

LMWH

There were 40 spinal hematomas reported after release of LMWH in 1993 in the U.S. in 5 years. The associated risk

factors include old age, female gender, traumatic placement, epidural greater than spinal, planned indwelling catheter, immediate preoperative LMWH dosing, early postoperative dosing, twice daily dosing, and concomitant medications. The consensus conference recommends delaying block placement for 10 to 12 hours after the last LMWH dose, and then delaying the first dose for greater than 24 hours after needle placement. Catheters should only be removed 10 to 12 hours after the last dose.

Warfarin

Patients on warfarin need to have stopped the medication several days before surgery. The consensus conference recommends stopping 4 to 5 days prior to the procedure, depending on the patient, the dose, and the level of anticoagulation maintained and documenting an INR less than 1.5 before proceeding. Furthermore, for patients who have taken prophylactic warfarin preoperatively and who have had the initial dose for more than 24 hours prior to procedure, it is recommended to check the PT/INR before the block. Catheters should only be removed 10–12 hours after the last dose of LMWH.

Antiplatelets

Antiplatement medications require various timeframes depending on the pharmacology of the individual drug. In general, NSAIDS are felt to be safe. Ticlopidine should be stopped a full 14 days prior to a procedure and clopidogrel for 7 days. For the intravenous glycoprotein IIb/IIIa inhibitors, it is recommended to stop abciximab for 24 to 48 hours, and to stop eptibifitide or tirofiban for 4 to 8 hours. These recommendations were based on clinical experience since there is no good data to support these conclusions.

Herbals

Garlic, ginseng, and ginko all inhibit platelets to varying degrees. It is generally felt that blocks are safe in the presence of these herbal preparations. However, in the presence of other anticoagulant or antiplatelet medications, the effect of herbal preparations on platelets may be additive and should be considered by the perioperative physician.

DTI and Fondaparinux Sodium

There is no information on these newer drugs. Decisions should be based on the pharmacological profile of each drug, patient risk factors, and procedural specific risk factors.

The decision to perform spinal or epidural anesthesia and the timing of catheter removal in a patient receiving antithrombotic therapy should be made on an individual basis, rather than a "cookbook" approach, weighing the small though definite risk of spinal hematoma with the benefits of regional anesthesia. Coagulation status should be optimized at the time of placement and removal, and the neurologic status and anticoagulation level continuously monitored.

SUMMARY

The use of chronic anticoagulation is becoming more common in general medical practice. More and more patients will be receiving long-term and/or lifelong anticoagulation. Surgeons and anesthesiologists need to become increasingly familiar with the monitoring of oral anticoagulation and must be familiar with the discontinuation of anticoagulation before and reinstitution after surgery. The appearance of low molecular weight heparin compounds and other drugs such as fondaparinux are simplifying the prevention of postoperative deep vein thrombosis. Improved methods of anticoagulating patients who develop postoperative deep vein thrombosis and pulmonary embolism are now in practice. Newer medications such as ximelagatran will be increasingly used due to their enhanced pharmacologic profiles. All these recent changes in the use of anticoagulants will have a direct effect on future surgical practice.

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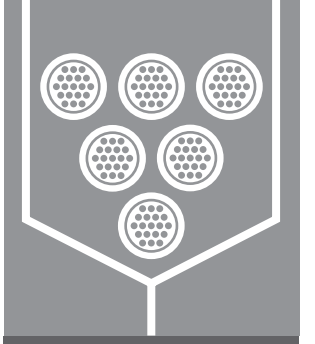

30

Pharmacological Approaches to Prevent or Decrease Bleeding in Surgical Patients

Jerrold H. Levy

The pathophysiology of bleeding during cardiac surgery and noncardiac surgery can be because of multiple causes. In cardiac surgical patient, cardiopulmonary bypass (CPB) and mediastinal suctioning can produce multiple hemostatic abnormalities with activation of the fibrinolytic cascade all contributing to the noted defect. Pharmacological approaches to reduce bleeding and transfusion needs are based on either preventing or reversing the defects associated with the coagulopathy (1–3). Because in vivo coagulation depends on suitable platelet–fibrinogen interactions, the eventual goal is to preserve normal coagulation function but to avoid pathological effects of hypercoagulability. Different pharmacological agents have been reported to decrease perioperative bleeding, especially after cardiac surgery, as shown in Table 30.1.

DESMOPRESSIN ACETATE

Desmopressin acetate (DDAVP) is a synthetic peptide with properties as shown in Table 30.2. It is a synthetic analogue of vasopressin created by substituting L-arginine for D-arginine, thus creating a drug with decreased vasopressor activity. DDAVP therapy causes a twofold to 20-fold increase in plasma levels of factor VIII and stimulates vascular endothelium to release the larger multimers of von Willebrand factor (vWF) (4). DDAVP also releases tissue plasminogen activator (tPA) and prostacyclin from vascular endothelium (4). Factor VIII is a plasma glycoprotein that speeds up activation of factor X by factor IXa in the presence of a phospholipid surface and calcium ions (5). Patients with hemophilia A have a variable decrease in plasma levels of factor VIII, and satisfactory levels of factor VIII also depend on the presence of adequate levels of vWF. vWF mediates platelet adherence to vascular subendothelium by functioning as a protein bridge between glycoprotein Ib receptors on platelets and subendothelial vascular basement membrane proteins. It also preserves plasma levels of factor VIII by protecting it from proteolytic enzymes and possibly by stimulating its synthesis (6). Patients who have von Willebrand disease have variable decreases in vWF levels, manifested by prolonged bleeding times (6).

Clinical Uses in Medical Conditions

DDAVP shortens the bleeding time of patients with mild forms of hemophilia A or von Willebrand disease (7). However, patients with severe von Willebrand disease have little vWF to release and therefore do not respond to administration of desmopressin (5). In addition, patients with a rare form of von Willebrand disease, type two B, have an exaggerated platelet response to release of vWF by

TABLE 30.1
PHARMACOLOGICAL APPROACHES REPORTED TO DECREASE BLEEDING

Desmopressin (DDAVP).
Aprotinin.
Fibrinolytic inhibitors: tranexamic acid, epsilon-aminocaproic acid.
Nafamostat.
Recombinant Factor VIIa.

DDAVP where platelets aggregate abnormally and are thus consumed, producing thrombocytopenia and worsening of hemostasis (8).

DDAVP has also been used to decrease bleeding and shorten bleeding times in various medical conditions (7,9–15). Kobrinsky (16) found that DDAVP was useful in shortening bleeding times of patients with aspirin-induced platelet dysfunction and patients with isolated platelet dysfunction. In addition, 18 of their patients treated with DDAVP and epsilon-aminocaproic acid underwent surgical procedures without needing blood products. Other researchers have also shortened bleeding times of patients with acquired and inherited forms of platelet dysfunction with DDAVP treatment (17–19).

Uremic patients may have abnormal hemostasis caused by platelet dysfunction. Cryoprecipitate, which supplies factor VIII and vWF, is partially effective therapy for patients with uremia. Researchers have shortened bleeding times in these patients by using DDAVP. They were successful and temporarily shortened bleeding times by using intravenous or intranasal DDAVP (17,19). In patients with hepatic cirrhosis, Agnelli et al. (20) gave DDAVP to a group of patients and increased the levels of vWF and therapy, shortening their bleeding times.

Clinical Uses During Surgical Procedures

Kobrinsky (16) normalized bleeding times in 42 patients with various bleeding disorders by using DDAVP therapy. Eighteen of these patients underwent various surgical procedures ranging from dental extractions to repair of coarctation of the aorta without needing the use of blood products. In 1987, Kobrinsky (21) also found decreased blood loss and decreased transfusion requirement in patients treated with DDAVP in a randomized double-blind trial of patients undergoing Harrington rod spine surgery. This group of patients should not have had preoperative platelet function abnormalities.

TABLE 30.2
PHYSIOLOGICAL PROPERTIES OF DESMOPRESSIN

Synthetic analogue of vasopressin.
V2 specific effects without vasopressor activity.
Stimulates vascular endothelium to release multimers of vWF, but tPA and prostacyclin are also released.
vWF mediates platelet adherence to vascular subendothelium.

Salzman et al. (14) performed a randomized double-blind trial in which DDAVP or placebo was administered after protamine administration to 70 patients undergoing various cardiac operations needing CPB. The group receiving DDAVP bled less (1317 ± 486 mL, mean ± SD) than the group receiving placebo (2210 ± 1415 mL) over the first 24 hours postoperatively. The DDAVP-treated group was also found to have higher plasma levels of vWF. However, because of the excessive amount of blood loss over 24 hours in both groups, there are important questions on the validity of the results of this study. In addition, the effects of DDAVP on transfusions are not reported in the study.

Efforts to confirm the original success with DDAVP therapy in cardiac surgical patients by Salzman et al. have not been consistently positive. Czer et al. (22) gave DDAVP to patients bleeding more than 100 mL per hr at least 2 hours after ending of CPB. Control subjects were treated by transfusion therapy. Those treated with DDAVP needed less blood products, especially platelets, while achieving similar decreases in bleeding. However, because this study was nonrandomized and unblinded, its results are also not accepted as proof that DDAVP is universally effective.

In 1988, Rocha et al. (13) reported a randomized double-blind trial of DDAVP in 100 patients at the conclusion of CPB after a trial septal defect repair or valvular replacement. There was no significant difference in overall blood loss between the DDAVP and the placebo group (131 versus 193 mL). Hackmann et al. (10) performed a double-blind randomized study comparing blood loss in patients undergoing primary coronary artery bypass grafting and/or valvular replacement with DDAVP or placebo. There was no difference in blood product transfusion rates or blood loss within the first 24 hours after surgery. In addition, postoperative use of blood products did not differ between the groups. This finding led the authors to infer that "most patients who undergo elective cardiac surgery receive no hemostatic benefit from the use of desmopressin" (10).

Which patients might benefit from use of DDAVP (23–26)? Patients with mild to moderate forms of hemophilia or von Willebrand disease undergoing surgery are likely to benefit from its use. In addition, patients with uremic platelet dysfunction and patients with chronic liver disease undergoing major surgery would benefit from DDAVP.

It is yet to be seen if patients taking aspirin or other antiplatelet therapy would benefit from its use, but it may be worth trying in this patient who is bleeding excessively after surgery. Mongan and Hosking (23) reported that patients with a thromboelastogram (TEG) taken after protamine administration and with maximal amplitude less than 50 mm benefit from the effects of DDAVP. This study used a method to separate patients with platelet dysfunction from those with acceptable activity. Patients with reduced platelet function bled significantly more than those whose TEG was near normal. DDAVP was administered to patients with abnormal platelet function (TEG less than 50 mm) and the chest tube output was similar to that seen with those who had normal platelet function. This study brings into question the mechanism of DDAVP, and perhaps elevating factor VIII and vWF are effective only in the presence of abnormal platelet function. Universal application of DDAVP would not be expected to yield consistent efficacy if only certain subpopulations of patients were treatable. Perhaps the original patient population utilized by Salzman et al. contained a high number of patients with significant postCPB platelet dysfunction. Some centers using TEG today do select patients with mild to moderate platelet dysfunction and target them for DDAVP therapy.

DDAVP is in some circumstances a marked releaser of tPA. It is well known that tPA rises during CPB and one has to wonder whether giving a tPA-releasing agent is counterproductive in some patients who are susceptible to tPA release. Recent work so far has not shown an advantage to combining DDAVP with a lysine analogue fibrinolytic inhibitor (tranexamic acid) (26). This study, like many others, was done in all covers and not isolated as was Mongan and Hosking's work to those with proved platelet dysfunction.

Administration

In the surgical patient, DDAVP should be administered intravenously. A dose of 0.3 mg per kg achieves maximal increases in levels of factor VIII and vWF in 30 to 60 minutes with no further increases achieved by higher doses. The drug, which is supplied in a 4 mg per mL preparation, should be diluted and given over 15 to 30 minutes to avoid hypotension. Although the drug has a half-life of 2.5 to 4.4 hours, repeated administration results in tachyphylaxis (5).

Undesirable Effects

Although few adverse effects are seen with the correct use of DDAVP, when given rapidly, it may cause flushing, hypotension, and increased heart rate, all attributable to vasodilatation because of release of prostacyclin from endothelial cells and direct effects on vascular smooth muscle (5,24). These effects may be avoided by giving the drug over 15 minutes or more. Because DDAVP has a potent antidiuretic effect and is given in doses 15 times greater than those used to treat diabetes insipidus, there is a potential for free water retention and hyponatremia (5). However, few cases of fluid overload or hyponatremic seizures have been reported, and the drug appears to be safe even in patients with uremia (25). Of concern have been case reports of arterial thrombosis in patients receiving DDAVP (27). Levi et al. (28) recently reported an increased risk of myocardial infarction (MI) in his meta-analysis of hemostatic agents. DDAVP's indication despite the above review remains in question.

APROTININ

Aprotinin (Trasylol) is a serine protease inhibitor derived from bovine lung (29). Among the proteases it can inhibit are trypsin, chymotrypsin, plasmin, tPA, serum urokinase plasminogen activator, and both tissue and plasma kallikreins (29). Because of its inhibition of trypsin and chymotrypsin, it was originally used clinically for treating acute pancreatitis. Although aprotinin was tried in the 1960s to decrease bleeding in cardiac surgical patients, its use was mostly therapeutic and only evaluated low doses to treat bleeding after surgery rather than to prevent it. However, a prophylactic high-dose technique was used subsequently that showed efficacy (30,31). The design of the study was to develop a pharmacological approach to inhibit inflammatory responses during CPB giving aprotinin as a loading dose of two million units after intubation and maintained therapeutic levels with a continuous infusion of 500,000 units per hr and a cardiopulmonary pump prime dose equal to the loading dose of two million units to compensate for the dilutional effects of extracorporeal circulation. Pulmonary dysfunction was not inhibited, but it was noted the chest tube drainage from the aprotinin patients was minimal. Multiple studies subsequently confirmed this effect (32–42). A summary of the studies investigating high-dose therapy in cardiac surgical patients are listed in Table 30.3.

In 20 patients undergoing heart transplantation, Havel et al. (43) reported lower chest tube drainage and transfusion requirements in treated patients using a two million unit dose administered after intubation and two million units added to the CPB circuit; 70% of aprotinin-treated patients did not receive allogeneic blood compared with 30% of control subjects. Morris (43a) reported 90 adult patients undergoing orthotopic heart transplantation with

TABLE 30.3

SUMMARY OF TRIALS COMPARING TREATMENT WITH HIGH-DOSE[a] APROTININ WITH NO TREATMENT OR PLACEBO IN PATIENTS UNDERGOING CARDIAC SURGERY WITH CARDIOPULMONARY CONDITIONS

			Mean Total Postoperative Chest Tube Loss (mL)		Mean Total Allogeneic Transfusion Requirement (% of Patients Who Did Receive Allogeneic Products)	
Reference	**Study Design**	**Surgical Procedure (No. Patients)**	**Aprotinin**	**Placebo**	**Aprotinin**	**Placebo**
Repeat cardiac surgery						
Bidstrup et al.	p	HVR(15) or CABG (9) repeat surgery	245	1979	0.2 u (83)	
Lemmer et al.	mc, p, r, pl, db, pc	CABG repeat surgery (55)	1225	1700	0.3 u	10.7
Levy et al.	mc, p, r, pl, db, pc	CABG repeat surgery (126)	900	390	2.2 u	10.3
Orchard et al.[b]	p, r, pl, db, pc	Valve repeat surgery	288	1509	1435 mL[c]	1959 ml
Royston et al.	p, r, pl.	Valve (18) or CABG (4) repeat surgery	286		0.5 u (64)	3.7
Primary cardiac surgery						
Alajmo et al.	p, r, pl	HVR (20) CABG (14)	486	830	213 mL	409
Baele et al.	p, r, pl, sb	CABG(75) valve (14) OTHER (26)[d]	699	1198	2.7 u	4.5u
Bidstrup et al.	p, r, p l, db, pc	CABG(77)	309	573	0.3 u	2.0
Bidstrup et al.	p, r, pl, db, pc	CABG(90)[e]	400	630	450 mL	795 ml
Dietrich et al.	p, r, pl, db, pc	CABG(39)	738	1431	0.6 u	2.3 u
Dietrich et al.	p, r, pl	CABG(1085) valve CABG + valve[f]	678	1037	942 mL	1999 ml
Harder et al.	p, r, pl, db, pc	CABG(80)	5599	911[g]	2.4 u	
Havel et al.	p, r, pl	CABG(22)	610	1000		3.
Lemmer et al.	mc, p, r, pl, db, pc	CABG(141)	855	1053	2.2 u	5.7 u
Swart et al.	p, r, pl, db, pc	CABG(50) valve	506	783	1.8 u	2.8 u
van Oeveren et al.	P, r, pl	CABG(22)	357	674	700 mL	1400 ml

[a]The standard high-dose regimen consisted of 280 mg (2 million KIU) intravenous loading dose after anesthesia induction followed by 70 mg/hr (500,000 KIU/hr) continuous infusion for the duration of the operation and 280 mg.
[b]Patients received standard high-dose aprotinin regimen with 140 mg instead of the usual 280 mg added to the CPB pump prime fluid.
[c]Results include total homologous and autologous blood products transfused.
[d]Includes repeat surgery, combined HVR and CABG, combined cardiac and vascular surgery, bivalvular surgery, and septal defect repairs.
[e]Results expressed as total median blood loss and transfusion requirements.
[f]Includes 201 patients who underwent repeat cardiac operations.
[g]Values expressed as milliliters of blood loss with a hemoglobin concentration of 7 mmol/L during the intraoperative and postoperative period.
P, prospective; me, multicentered; r, randomized; db, double blind; p1, parallel; pc, placebo controlled; sb, single blind; u, units; CABG, coronary artery bypass.

preoperative elevated international normalized ratios. Most of these patients had received aprotinin, almost 20% received no blood products in the first 24 hours following surgery, and there were no correlations between INR and chest tube output.

Mechanisms of Action

Aprotinin's broad spectrum of protease inhibition provides multiple potential mechanisms for decreasing bleeding and inflammation. (Table 30.4) In cardiac surgery and CPB, its ability to reduce bleeding and the need for transfused blood is by inhibiting of plasmin formation/activity and kallikrein. By inhibiting plasmin, the active proteolytic enzyme of the fibrinolytic system, aprotinin is able to inhibit fibrinolysis. In addition, by inhibiting kallikrein, which helps to amplify and accelerate contact activation of factor XII (Hageman factor) to XIIa, activation of the intrinsic pathway of coagulation is inhibited or attenuated. By inhibiting kallikrein, aprotinin likely alters potential adverse effects of contact activation and potentially protect platelets from activation. Kallikrein in itself is also an activator of the fibrinolytic system, and therefore by inhibiting kallikrein, aprotinin inhibits fibrinolysis in a manner that is independent of its capacity to inhibit plasmin. Van Oeveren et al. (44) postulated that aprotinin inhibits the

TABLE 30.4
CHEMICAL PROPERTIES OF APROTININ

Basic polypeptide (pKa 10)
Molecular mass 6512 Da
Derived from cow lung
Nonspecific protease inhibitor of trypsin, kallikrein, plasmin
Activity expressed as kallikrein inactivator units (KIU)

plasmin-related degradation of the platelet glycoprotein Ib receptor.

The precise mechanism of action of aprotinin in reducing blood loss and transfusion requirement is not clear, and the optimal dose is not known. Further studies are needed to reveal how this drug decreases blood loss in patients undergoing CPB. However, seemingly whatever the mechanism is, the result is a better functioning platelet possibly because of preservation of the glycoprotein Ib receptor, which mediates adhesion of platelets to vWF (44,45). Aprotinin is also thought to exhibit unique antiinflammatory effects; these effects are important as an increasing favorable effect in CPB. Aprotinin blocks neutrophil activation and mobilization, and protease activated receptors (PAR), to prevent potential pathological effects of thrombin mediated inflammation.

Dosage Schedules

The biological activity of aprotinin is expressed in kallikrein inactivator units (KIU), where one inactivator unit is defined as that quantity that inhibits one unit of kallikrein. The original *Hammersmith regimen*, recommends giving a loading dose (for a 70 kg adult) of 280 mg (2,000,000 KIU) over 20 minutes, followed by an infusion of 70 mg per hr (500,000 KIU) and an additional 280 mg (2,000,000 KIU) in the CPB pump prime (31). Using this dosage regimen, Bidstrup et al. (32) were able to achieve plasma concentrations greater than 4 mmol per L, a concentration recommended by Fritz and Wunderer (47) to inhibit both plasmin and plasma kallikrein (31). Levy (48) reported elimination half-lives to be approximately 5 hours, and based on their pharmacokinetic calculations, a full Hammersmith dose regimen would produce 200 KIU per mL. Different studies as listed in Table 30.4 have shown the full-dose technique to be effective. Multiple adjustments and dosing regimens have been tried to reduce drug costs and evaluate efficacy (Table 30.5). Studies using lower doses than those used in the Hammersmith regimen have reported variable results. Further, the safety data that exists with aprotinin from the clinical studies that lead to approval of the drugs were mostly with full dose techniques.

One of the noteworthy safety and efficacy studies was reported by Levy et al. (52) evaluating four different treatment groups in 287 patients undergoing repeat myocardial revascularization. The four groups were high-dose aprotinin, consisting of 2,000,000 KIU aprotinin loading dose, 2,000,000 KIU added to the CPB circuit prime, and a continuous infusion of 500,000 KIU during surgery; low-dose aprotinin, consisting of 1,000,000 KIU aprotinin loading dose, 1,000,000 KIU added to the CPB circuit prime, and a continuous infusion of 250,000 KIU per hr during surgery; pump prime aprotinin only, consisting of 2,000,000 KIU aprotinin added to CPB circuit prime; and placebo. The number of units of allogeneic packed red blood cells was significantly less in the aprotinin-treated patients than in placebo patients (high dose, 1.6 units; low dose, 1.6 units; pump prime only, 2.5 units; placebo, 3.4 units). There

TABLE 30.5
SUMMARY OF TRIALS COMPARING TREATMENT WITH LOW-DOSE (50% OF HIGH-DOSE REGIMEN) APROTININ (APR) WITH HIGH DOSE[a] OR PATIENTS UNDERGOING CARDIAC SURGERY WITH CPB

Reference	Study Design	Surgical Procedure (number of Patients)	Treatment Regimen	Mean Total Postoperative Blood Loss (mL)
Cosgrove et al.	p, r, pl, db, pc	CABG repeat surgery (169)[b]	Aprl high-dose regimen Apr2 50% of high-dose regimen PL	720[c] 866[c] 1121
Levy et al.	me, p, r, pl, db, pc	CABG repeat surgery (254)	Aprl high-dose regimen Apr2 50% of high-dose regimen Apr3 280mg added to CPB pump prime fluid PL	900** 1040** 1420 1700
Liu et al.	p, r, pl, db, pc	CABG (40)	Apr 50% of high-dose regimen PL	674** 1086

[a]The standard high-dose regimen consisted of 280 mg (2 million KIU) intravenous loading dose at induction followed by 70 mg/hr (500 000 KIU/hr) continuous infusion for the duration of the operation and 280 mg (2 million KIU) added to the CPB pump prime fluid.
[b]Twenty-one percent of patients received preoperative aspirin (acetylsalicylic acid).
[c]Statistically significant differences in blood loss ($P = .001$), transfusions requirements ($P = .006$), and patients transfused ($P = .001$) were reported between aprotinin recipients (results from high-dose and low-dose regimens combined) and placebo recipients.

were even greater reductions in total blood product exposure in high-dose and half-dose groups compared with placebo or pump prime. There were no differences in treatment groups for the incidence of perioperative myocardial infarction.

Safety Profile of Aprotinin

From the large number of patients that have received aprotinin in European studies, few adverse effects have been reported. However, in the study performed by Cosgrove et al. (42) in patients undergoing repeat myocardial revascularization, they found only a trend toward a higher incidence of myocardial infarction and postoperative increases in serum creatinine levels in the aprotinin-treated groups, although these trends were not statistically significant. Other studies have not found any statistical differences in the incidence of these complications. van Oeveren et al. (44) in almost 2,000 patients noted no difference in intensive care unit stay time to extubation, congestive heart failure, or other surrogate markers for myocardial infarction in patients treated with aprotinin. (See Graft Patency.)

Heparin Management During Use of Aprotinin

The celite-activated activated clotting time (ACT), a common test to measure anticoagulation, is prolonged by aprotinin (29). Wang et al. (54) reported the celite-activated ACT, but not the kaolin-activated ACT, was prolonged in the presence of aprotinin. Kaolin absorbs 98% or greater available aprotinin within seconds of contact. Therefore, any effect that aprotinin would have upon ACT is negated in kaolin-based ACT as long as the aprotinin dosage is not increased beyond a full Hammersmith dose. This led to speculations the trend toward a higher incidence of myocardial infarction in Cosgrove's study was because of inadequate heparinization, because in that study the celite-activated ACT was kept at only a minimum of 400 seconds even in the presence of aprotinin. If a Kaolin-activated ACT had been used, the ACTs measured in that study would probably have been found to be significantly lower. Since this, several recommendations have surfaced. Hunt et al. (55) and Royston recommended keeping the ACT greater than 750 during CPB if the celite-activated ACT is used (31). Wang (54) recommended the celite-activated ACT should not be used at all in the presence of aprotinin. They recommend using only Kaolin-activated ACTs. One suitable method to keep appropriate levels of anticoagulation is to give added doses of 100 U per kg heparin every hour in a fixed dosing scheme after the first loading dose of heparin. Alternately, based on clinical studies, using heparin monitoring systems, the heparin level should be kept $\geq$2.7 units per ml. Because of the controversy about the correct heparin dose and ACT for patients undergoing CPB even without aprotinin, fixed doses of heparin every hour (or half hour) during CPB represent a clinically useful method for heparin administration if other monitors of heparin levels are not available. Kaolin-activated ACT is an acceptable method for monitoring even in the presence of aprotinin, and it appears that a controversy will rage for some time about whether the celite-based ACT prolongation represents a problem or further anticoagulation because of aprotinin. Heparin dosing should not be reduced in the presence of aprotinin.

Use in Children

Dietrich (56) compared the clinical efficacy of high-dose and low-dose aprotinin for congenital heart surgery using a 4.2 or 2.1 mg per kg intravenous bolus dose administered after anesthesia induction and 4.2 or 2.1 mg per kg added to the CPB pump prime fluid in 60 children weighing less than 10 kg. Postoperative blood loss at 6 hours was lower in the high-dose group than in the low-dose and control groups, but no differences were observed in either the blood loss at 24 hours or in overall homologous transfusion requirements. Compared to 100 historical control patients, postoperative blood loss (154 versus 210 mL) and intraoperative (758 versus 1071 mL) and postoperative (53 versus 130 mL) transfusion requirements were significantly lower in 105 aprotinin-treated children. These children received 4.9 to 7.0 mg per kg intravenous loading dose after anesthesia induction followed by 2.8 to 4.2 mg/kg/hr continuous infusion and 4.9 to 7.0 mg per kg added to the CPB pump prime fluid.

Boldt et al. (57) reported lower aprotinin doses (3.5 mg per kg intravenous loading dose followed by 3.5 mg/kg/hr continuous infusion and 3.5 mg per kg added to the CPB pump prime fluid) in 48 children. No improvements in postoperative blood loss or transfusion requirements were reported among the children less than or more than 10 kg, with and without aprotinin. Higher blood transfusion volumes in children weighing less than or more than 10 kg and postoperative blood loss in children weighing more than 10 kg were noted in aprotinin-treated patients. Boldt et al. (58) also compared high-dose (4.9 mg per kg intravenous loading dose administered after induction followed by 1.4 mg/kg/min continuous infusion and 4.9 mg per kg added to the CPB pump prime fluid) and low-dose (2.8 mg per kg intravenous loading dose administered after anesthesia induction followed by 2.8 mg/kg/hr continuous infusion and 2.8 mg per kg added to the CPB pump prime fluid) regimens with those of control patients. Forty-two

children weighing less than 20 kg undergoing cardiac surgery took part in the study, and similar postoperative blood losses and transfusion requirements were found in all three treatment groups. In an adult weighing 80 kg, equivalent dosages to those used in the last trial would largely exceed the clinically effective high-dose aprotinin regimen normally administered to adults. This shows the difficulty in extrapolating drug doses in adults to infants and children. Although aprotinin has displayed clinical efficacy in some pediatric trials, the drug appears to be less effective in infants and small children in reducing allogeneic blood transfusions than in adults (56). Because of the severe dilutional changes that occur and obligate requirement of transfusion in small children and even adults, this may explain in part the difficulty in proving efficacy in this patient population.

Miller et al. (59) reported the hemostatic and economic effects of aprotinin in children undergoing reoperative cardiac procedures with cardiopulmonary bypass. Patients were randomized to control, low-dose aprotinin, and high-dose aprotinin groups were established with 15 children per group. Platelet counts, fibrinogen levels, and thromboelastographic values at baseline and after protamine sulfate administration, number of blood product transfusions, and 6-hour and 24-hour chest tube drainage were used to evaluate the effects of aprotinin on postbypass coagulopathies. Time needed for skin closure after protamine administration and lengths of stay in the intensive care unit and the hospital were recorded prospectively to determine the economic impact of aprotinin. Coagulation tests performed after protamine administration rarely showed fibrinolysis but did show significant decreases in platelet and fibrinogen levels and function. The thromboelastographic variables indicated a preservation of platelet function by aprotinin. Decreased blood product transfusions, shortened skin closure times, and shortened durations of intensive care unit and hospital stays were found in the aprotinin groups, most significantly in the high-dose group with a subsequent average reduction of nearly $3,000 in patient charges. The authors conclude that in children undergoing reoperative cardiac surgical procedures, aprotinin is effective in attenuating postbypass coagulopathies, decreasing blood product exposure, improving clinical outcome, and reducing patient charges.

Effects on Graft Patency and Perioperative Myocardial Infarction

Potentially any drug that decreases bleeding and transfusion requirements has the potential to affect graft patency. The effects of aprotinin have been assessed in two randomized, double-blind, prospective, placebo-controlled studies in patients who underwent CABG surgery. Bidstrup et al. (38) reported vein graft patency 7 to 12 days postoperatively by magnetic resonance imaging in 90 patients who underwent primary CABG surgery. There were no differences between treatment and control groups and 46 evaluated internal mammary artery (IMA) grafts were patent. Lemmer et al., (36) using ultrafast computed tomography to assess vein and IMA graft patency 7 to 60 days after primary CABG surgery in 151 patients or repeat CABG surgery in 65 patients, found no statistically significant differences, although there was a trend toward lower vein and IMA graft patency rate in aprotinin recipient patients. Lemmer also reported perioperative myocardial infarction and found no significant differences in patients between groups. Levy et al. (52) reported their results from a randomized prospective study of repeat coronary artery bypass surgical patients evaluating perioperative myocardial infarction in full-dose and half-dose aprotinin-treated patients using a blinded core laboratory to evaluate 24-hour serial creatine phosphokinase myocardial band (CPK-MB) levels and electrocardiograms. The rate of myocardial infarction was not statistically different in high-dose, low-dose, pump-prime only, and placebo groups.

Alderman (58a) reported a prospective study that evaluated the effects of aprotinin on graft patency, prevalence of MI, and blood loss in patients undergoing primary coronary surgery with cardiopulmonary bypass (IMAGE study). Patients from 13 international sites were randomized to receive aprotinin (n = 436) or placebo (n = 434). Graft angiography was obtained a mean of 10.8 days after the operation. Electrocardiograms, cardiac enzymes, and blood loss and replacement were evaluated. In 796 assessable patients, aprotinin reduced thoracic drainage volume by 43% ($P < .0001$) and requirement for RBC administration by 49% ($P < .0001$). Among 703 patients with assessable saphenous vein grafts, occlusions occurred in 15.4% of aprotinin-treated patients and 10.9% of patients receiving placebo ($P = .03$). After adjusting risk factors associated with vein graft occlusion, the aprotinin versus placebo risk ratio decreased from 1.7 to 1.05 (90% confidence interval, 0.6 to 1.8). These factors included female gender, lack of prior aspirin therapy, small and poor distal vessel quality, and possibly use of aprotinin-treated blood as excised vein perfusate. At U.S. sites, patients had characteristics more favorable for graft patency, and occlusions occurred in 9.4% of the aprotinin group and 9.5% of the placebo group ($P = .72$). At Danish and Israeli sites, where patients had more adverse characteristics, occlusions occurred in 23.0% of aprotinin-treated and 12.4% of placebo-treated patients ($P = .01$). Aprotinin did not affect the occurrence of MI (aprotinin: 2.9%; placebo: 3.8%) or mortality (aprotinin: 1.4%; placebo: 1.6%).

Effects on Renal Function

Because aprotinin undergoes active reabsorption by the proximal tubules, aprotinin effect on renal function has been examined. Bidstrup et al. (32) reported higher mean urine output in aprotinin compared with placebo treatment in 80 patients who underwent primary CABG surgery. Blauhut et al. (34) reported that osmolar clearance and fractional sodium excretion were higher in 13 aprotinin-treated patients compared with 13 control subjects after primary CABG. However, there were no differences in creatinine concentrations, electrolytes, or creatinine clearance between the two treatment groups. Lemmer et al. (60) also reported no differences in renal function in aprotinin-treated versus placebo-treated patients from recent U.S. studies. In patients undergoing thoracic or thoracoabdominal aortic surgery requiring CPB and hypothermic arrest, an increased risk of renal dysfunction was reported, described as an elevation of plasma creatinine greater than 1.5 preoperative values (61). The authors compared their data to 20 historical control subjects but found greater incidence of renal failure. However, the patients receiving aprotinin also received significantly lower doses of heparin compared with their historical control subjects (61).

Meta-analysis

Levi et al. (28,62) reported a meta-analysis of all randomized, controlled trials of the three most often used pharmacological strategies to decrease perioperative blood loss (aprotinin, lysine analogues (aminocaproic acid and tranexamic acid), and desmopressin) . Studies were included if they reported at least one clinically relevant outcome (mortality, rethoracotomy, proportion of patients receiving a transfusion, or perioperative myocardial infarction) as well as perioperative blood loss. In addition, a separate meta-analysis was done for studies about complicated cardiac surgery. They identified 72 trials (8,409 patients) that met the inclusion criteria. Treatment with aprotinin decreased mortality almost two-fold (odds ratio 0.55 (95% CI 0.34 to 0.90)) compared with placebo. Treatment with aprotinin and with lysine analogues decreased the frequency of surgical reexploration (0.37 (0.25 to 0.55), and 0.44 (0.22 to 0.90), respectively). These two treatments also significantly decreased the proportion of patients receiving any allogeneic blood transfusion. By contrast, the use of desmopressin resulted in a small decrease in perioperative blood loss, but was not associated with a beneficial effect on other clinical outcomes. Aprotinin and lysine analogues did not increase the risk of perioperative myocardial infarction; however, desmopressin was associated with a 2.4-fold increase in the risk of this complication. Studies in patients undergoing complicated cardiac surgery showed similar results. The authors suggest that pharmacological strategies that decrease perioperative blood loss in cardiac surgery, in particular aprotinin and lysine analogues also decrease mortality, the need for rethoracotomy, and the proportion of patients receiving a blood transfusion.

Hypersensitivity Reactions

As a xenogeneic protein (bovine derived), aprotinin can cause anaphylaxis. Dietrich (63) reported the prevalence of adverse reactions to reexposure to high-dose aprotinin in patients undergoing cardiac surgery in Germany between 1988 and 1995 with at least two exposures. There were 248 re-exposures to aprotinin in 240 patients: 101 adult and 147 pediatric cases. The time between the first and second aprotinin exposures was 344 (interquartile range 1,039) days, and 7 reactions to aprotinin were reported (2.8%) that ranged from mild to severe. Patients with an interval less than 6 months since the previous exposure had a statistically higher incidence of adverse reactions than patients with a longer interval (5/111 or 4.5% versus 2/137 or 1.5%, $p < 0.05$). Two patients reacted to a test dose of 10,000 KIU aprotinin. The authors recommend for reexposure to aprotinin: (a) delay of the first bolus injection of aprotinin until the surgeon is ready to begin cardiopulmonary bypass, (b) test dose of 10,000 KIU aprotinin in all patients with aprotinin treatment, (c) H1/H2 blockade in known or possible reexposure, and (d) avoidance of reexposure within the first 6 months after the previous exposure to aprotinin. The authors also suggest reexposure to aprotinin in patients with a high risk of bleeding is justified, because the benefits of aprotinin treatment outweigh the relative risk of a serious allergic reaction.

In children undergoing cardiac surgery in a retrospective review of aprotinin (n = 865) administration, 681 first exposures, 150 second exposures, and 34 third or higher exposures were examined (64). Reactions were classified as mild (generalized cutaneous erythema,) or severe (unexplained cardiopulmonary instability after aprotinin exposure). Records of patients sustaining a reaction were reviewed to assess the impact of the reaction on outcome and to survey reaction management strategies. Reactions occurred in seven of 681 first exposures (1.0%), of which two were minor and five were severe. In second exposures, there were reactions in two of 150 (1.3%), of which both were severe. In 34, third or higher exposures, there was only one reaction (2.9%), which was severe. Reactions were no more likely on second, third, or higher exposure than on initial exposure. Skin testing had a negative predictive value of 98.9% and a positive predictive value of 20%. Anti-aprotinin IgE was undetectable in seven of eight reactor cases tested. No adverse sequelae were attributed to aprotinin reaction.

The preoperative prevalence of aprotinin-specific antibodies in patients scheduled for cardiac operations (65) were reported from sera of 520 consecutive cardiac surgical patients were collected preoperatively and screened retrospectively for aprotinin-specific IgG using a standard enzyme-linked immunosorbent assay (ELISA). Positive sera were analyzed also for aprotinin-specific IgA (ELISA) and IgE (fluorescence enzyme immunoassay). The histories of all patients were reviewed with focus on aprotinin preexposure. Of 520 patients, 22 (4%) had specific IgG. Only three of these had a documented aprotinin preexposure. Of 448 patients exposed to aprotinin intraoperatively, 15 had preformed specific antibodies. The only patient presenting with severe anaphylaxis was positive for both IgG and IgE, and had a recent IV preexposure in cardiovascular surgery. The presence of aprotinin-specific IgG alone seems not to induce adverse reactions on exposure. Exposure history alone is not sensitive enough to identify patients with aprotinin-specific antibodies. The clinical significance of preformed aprotinin-specific IgG remains questionable, whereas preformed IgE was present in the only patient who suffered from severe anaphylaxis on reexposure to aprotinin.

Non-Cardiac Surgical Patients

Aprotinin has also been studied for its ability to decrease bleeding and transfusion requirements after total hip replacement procedures. In these studies, aprotinin has decreased bleeding and transfusion requirements without an increased risk of postoperative thromboembolic complications (66,67). After total hip replacement, patients are at a greater risk for postoperative thromboembolic complications. The lack of increased deep vein thrombosis in this patient population supports the lack of prothrombotic effects of aprotinin (66,67).

LYSINE ANALOGUES AND ANTIFIBRINOLYTIC THERAPY

Epsilon-aminocaproic acid (EACA, Amicar) and its analogue, tranexamic acid (AMCA), are derivatives of the amino acid lysine (Fig. 30.1). Both drugs inhibit the proteolytic activity of plasmin and the conversion of plasminogen to plasmin by plasminogen activators as shown in Table 30.6. Their role in the pharmacological prevention of bleeding for cardiac surgery is reviewed.

The Fibrinolytic System

The fibrinolytic system inhibits the formation of intravascular fibrin, maintains fibrin localized to bleeding sites, and restores blood flow in obstructed vessels (Fig. 30.1).

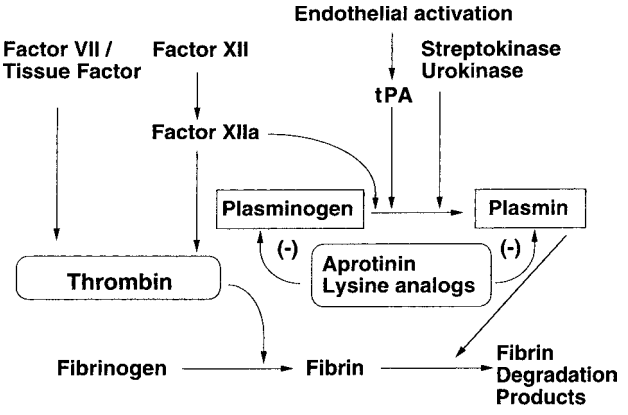

Figure 30.1 Coagulation and fibrinolytic pathways for initiation and inhibiting. Thrombin generation will convert fibrinogen to fibrin but also serves as an endothelial activator for tPA release. Contact activation via factor XIIa generation also converts plasminogen to plasmin. Aprotinin, a protease inhibitor, and lysine analogues epsilon-aminocaproic acid and tranexamic acid inhibit plasminogen and plasmin.

Plasminogen is the precursor of plasmin, the main proteolytic enzyme of the fibrinolytic system. It is a polypeptide consisting of 790 amino acids that has a unique conformation with five triple-loop regions called kringles, because of their resemblance to a Scandinavian biscuit of the same name (68). These kringles form binding sites for lysine and are responsible for binding fibrin, fibrinogen, factor V, factor VIII, platelet glycoprotein Ib, and complement. When activated by tPA, thrombin, kallikrein, urokinase, or streptokinase, plasminogen undergoes cleavage of two or more peptide bonds to become plasmin, a two-chain molecule linked by disulfide bonds. In the active form, plasmin is then able to lyse both fibrin and fibrinogen.

Fibrinogen is a dimer made of three polypeptide chains, synthesized in the liver, organized in mirror image, and bridged together by covalent disulfide bonds (69). Each side of this bond consists of three different polypeptide chains with distinct amino acid sequences. When thrombin is formed, it binds to the disulfide bonds, releasing fibrinopeptides A and B from the fibrinogen molecule, thus forming active fibrin, which then stacks together with other fibrin molecules that are then cross-linked at the alpha and gamma chains by factor XIII forming the fibrin mesh (69).

TABLE 30.6
CHEMICAL PROPERTIES OF FIBRINOLYTIC INHIBITORS

Low-molecular-weight molecules
Lysine analogues
Attach to the lysine binding site of plasmin(ogen)

Plasmin cleaves fibrinogen by initially removing peptides from the A alpha chain and then from the B beta chains, leaving what is called fragment X. This fragment undergoes asymmetric cleavage of all three chains, releasing fragment D and leaving fragment Y (69). The three chains remaining in fragment Y undergo further cleavage, releasing one more fragment D, thus leaving a core called fragment E, a dimer that contains parts of all three fibrinogen chains (69).

Attack by plasmin or fibrin results in different end products because of the fact that the fibrin monomers are polymerized and cross-linked by the activated factor XIII (68). The major difference in the end products of fibrin digestion in contrast to fibrinogen digestion is the release of the cross-linked complex of two D fragments called the D-dimer. In addition, initial degradation of cross-linked fibrin results in X-oligomers that are X fragments bound together by polymerization and cross-linking (68).

Plasmin has also been shown to decrease the activity of factors V, VIII, and IX. Plasmin also can activate complement via the C1 esterase (62). However, the main clinical implications result from the breakdown of existing fibrin and fibrinogen. Plasmin is a potent platelet inhibitor at normothermia, but at hypothermia (less than 32°C), it is a platelet activator. The mechanism of this platelet effect is unclear, but this is thought to be important in the overall mechanism of CPB coagulopathy. Therefore, either the formed clot is broken down or formation of a further clot is inhibited. In addition, the breakdown products of the lysis of fibrinogen and fibrin have little or no clotting capacity, whereas they increase vascular permeability, inhibit platelet aggregation, and interfere with the formation of the fibrin mesh.

Fibrinolysis During Cardiac Surgery

Fibrinolytic activity is initiated by incision and sternotomy, augmented by CPB, and peaks toward the end of extracorporeal circulation (70). Evidence for bypass-associated fibrinolysis has been shown by the presence of fibrin split products during and after CPB. Serum levels of tPA, an activator of plasmin released from endothelium, increase during CPB. In addition, plasminogen levels have been found to decrease at the same time that plasmin levels are increasing, indicating activation of plasminogen to plasmin.

The Lysine Analogue Antifibrinolytic Agents

Drugs that inhibit activation of plasminogen to plasmin and interfere with the lysis of fibrinogen and fibrin are called antifibrinolytic or antiplasmin agents (Table 30.6). They are omega aminocarboxylic acid analogues of lysine that bind to the kringles on plasminogen and plasmin, occupying the binding site for fibrinogen and fibrin and therefore interfering with the fibrinolytic process (68). Both EACA (Amicar) and trans p-amino methylcyclohexane-carboxylic acid (tranexamic acid) have been used to decrease fibrinolysis during cardiac surgery. Other analogues of lysine have been studied. Tranexamic acid is six to 10 times more potent than EACA (68).

Most early studies using antifibrinolytic agents showed decreased mediastinal drainage in patients treated with EACA. However, many of these studies lacked control subjects and were retrospective and unblinded. In 1967, Sterns and Lillehei (73) gave EACA to 240 patients at the end of CPB and again in the event of large amounts of blood loss. Compared with a historic group of 100 patients, the EACA-treated group had decreased blood loss.

In 1974, McClure and Izsac (74) published a double-blind randomized study of 71 patients with cyanotic and noncyanotic cardiac defects requiring CPB. In this study, EACA was infused from the time of chest opening and then for 24 hours. Those receiving EACA showed less bleeding from the time of termination of CPB, until the end of surgery, and the difference in bleeding was more pronounced in patients with cyanotic cardiac defects and those requiring a prolonged period of CPB.

In 1988, Vander Salm et al. (75) administered either EACA or placebo to 60 patients undergoing first-time CABG before protamine administration and then they were given an infusion of the drug for 6 hours. Patients that received EACA bled less than the control subjects in the first 12 postoperative hours (273 versus 332 mL). In addition, those receiving EACA had higher platelet counts and shorter bleeding times than those receiving placebo. However, no data regarding blood product transfusions were reported.

In a large, randomized, blinded study of 350 patients undergoing routine CABG, Del Rossi et al. (76) reported a significant decrease in blood loss in the first 24 postoperative hours in those patients receiving a 5 g loading dose followed by a 1 g per hr infusion during the next 6 to 8 hours, starting before skin incision. Not only was blood loss reduced in the EACA versus placebo group (617 versus 883 mL), but transfusion of packed red blood cells was also reduced (2.8 versus 4.2). There were no differences in myocardial infarction, cerebrovascular accidents, or graft failures in those receiving EACA compared with those receiving placebo, although the overall complication rate was low.

Horrow (77–79) also studied the use of tranexamic acid given in a prophylactic manner before skin incision for primary CABG surgery. In one study, 12-hour postoperative blood loss was 496 mL in the tranexamic acid group

compared with 750 mL in the placebo group (77). However, transfusion use was not different. Patients who received tranexamic acid had lower levels of fibrin split products and decreased plasminogen availability postoperatively. In a separate study, they again found decreased blood loss in patients receiving tranexamic acid compared with those receiving placebo but found no increased benefit by giving DDAVP concurrently (78). Efforts continue to decide the best dose using loading doses before incision of 2.5 to 40 mg per kg and one tenth the loading dose hourly for 12 hours, as reported in 148 patients (79). Larger doses did not further decrease bleeding.

Rousou (80) reported a clinical series of 415 consecutive patients undergoing primary CABG surgery where 209 received in the second 6 months of the study tranexamic acid as a 2 g bolus before the beginning of CPB and in 206, 8 g was given by slow infusion during bypass. In the patients who received tranexamic acid, there was a decrease in chest tube drainage from 1,114 to 803 mL in the treated patients and small, but statistically significant, differences in allogeneic blood product use for red blood cells (1.7 to 0.69 units per patient), fresh frozen plasma (0.23 to 0.024 units per patient), and platelets (1.06 to 0.3 units per patient). There were no differences in postoperative complications, although all data were collected by retrospective detailed chart reviews. The incidence of postoperative myocardial infarction was also low in both retrospective analysis (1% in controls versus 1.5% in the treated. patients). One should note the study was not blinded and no strict transfusion algorithm or guidelines were reported.

Pharmacology of EACA and Tranexamic Acid

Because of their likeness to lysine, EACA and tranexamic acid attach to the lysine binding sites on plasminogen and plasmin to inhibit binding of lysine residues on fibrinogen and fibrin by plasminogen and plasmin. Because plasmin(ogen) is now unable to bind to fibrin(ogen), it is unable to lyse it. Tranexamic acid is six to10 times more potent than EACA, probably because of subtle changes in the molecular structure that mimics lysine.

All antifibrinolytic drugs are water soluble and are therefore distributed through both the intravascular and extravascular compartments. Renal excretion accounts for most elimination of these drugs, with 80% to 90% of the drug recovered in the urine within 12 hours. Because of this method of elimination, urine levels of the drug can reach 50 to 100 times the plasma levels of the drugs.

Some studies reporting increased efficacy of administering antifibrinolytics have started therapy before skin incision. Recovered EACA loading doses of 5 to 10 g (around 75 to 150 mg per kg) should be given over 15 to 30 minutes, followed by an infusion of 10 to 15 mg/kg/hr. Tranexamic acid should be administered with loading doses of around 1 g (10 to 15 mg per kg) followed by an infusion of 1 mg/kg/hr. Even higher doses of tranexamic acid using 5 to 10 g have been reported in preliminary studies (29). These infusions are routinely continued until the end of CPB or surgery. Because tPA production is greatest during CPB and is rapidly cleared after weaning, lysine analogues should not be routinely continued into the intensive care unit unless there is bleeding or fibrinolysis is demonstrated.

Undesirable Effects of Antifibrinolytic Drugs

When administered intravenously to patients undergoing cardiac surgery, the adverse effects of antifibrinolytic agents are relatively infrequent. The most common side effect is hypotension during rapid intravenous administration. It is therefore recommended the intravenous loading doses be administered over 15 to 30 minutes with the patient in the supine position. Patients receiving these medications orally experience much more common side effects. Nausea, vomiting, diarrhea, and anorexia appear to be caused by a direct gastrointestinal irritation and are not related to plasma concentrations of the antifibrinolytic agents. Other side effects that have been reported after oral administration include nasal stuffiness, myalgias, muscle weakness, myoglobinuria, and skin rash.

Other undesirable effects seen after administration of antifibrinolytic agents are a direct result of inhibiting the fibrinolytic system. There is no definite evidence that EACA, tranexamic acid, or any of the antifibrinolytic agents can produce thrombosis. However, fibrin formed intravascularly will be resistant to lysis by the fibrinolytic system, which normally inhibits formation of and removes intravascular fibrin. There are reports in the literature of glomerular capillary thrombosis, renal cortical necrosis, deep venous thrombosis, and pulmonary embolism, with renal, carotid, and cerebral artery thrombosis (72). In addition, there is a report of widespread arterial and venous thrombosis in a patient with disseminated intravascular coagulation, a setting where use of antifibrinolytic therapy is dangerous and may be contraindicated (72).

In the literature dealing with the use of antifibrinolytic therapy during cardiac surgery, there have been no reported differences in the incidence of thrombotic complications between patients receiving antifibrinolytic agents and those receiving placebo, although the design of these studies has not been prospective. The incidence of perioperative myocardial infarction and stroke has not been reported as different in the treatment group as compared with control subjects. However, because of the low incidence of these complications in routine CABG surgery and the small

numbers of patients studied, one would be surprised to find any difference with small sample sizes. Prospective studies evaluating safety issues, including the risk of perioperative myocardial infarction, graft patency, and renal dysfunction, still need to be conducted, and although inhibiting fibrinolysis represents an effective way to reduce bleeding and transfusion needs, other issues need to be addressed. Tranexamic acid is approved for use in the United States to prevent bleeding in patients with hereditary angioedema undergoing tooth extraction, but no U.S. Food and Drug Administration indication for use in CPB has been approved. Most work has focused on the use of lysine analogues in first-time CABG. Comparative research between aprotinin and these agents in complex cases, the case mix where hemorrhage is the greatest problem, is required. Such studies are underway today at multiple institutions.

COMPARISON STUDIES

There is a lack of literature available to compare the efficacy and safety of pharmacological agents available for reducing allogeneic blood administration in cardiac surgical patients. Rocha et al. (13) compared aprotinin to DDAVP in 109 patients undergoing both CABG and valve operations. Aprotinin decreased blood loss and the need for transfusions, whereas DDAVP had no beneficial effect. Blauhut et al. (82) compared aprotinin to tranexamic acid in 43 patients undergoing CABG first-time surgery. Aprotinin reduced blood loss and transfusion requirements, but tranexamic acid failed to show a significant effect.

Because the results of previously reported small randomized clinical trials comparing EACA with aprotinin were inconclusive, Munoz (83) performed a meta-analysis to compare the relative effectiveness and adverse-effect profile. The authors took information from 52 randomized clinical trials published between 1985 and 1998 involving the use of epsilon-aminocaproic acid (n = 9) or aprotinin (n = 46) in patients undergoing cardiac surgery. The primary outcomes were total blood loss, red blood cell transfusion rates and amounts, reexploration, stroke, myocardial infarction, and mortality. Unfortunately, there were five times as many aprotinin studies as there were EACA studies, and most of the EACA studies report primary CABG patients who do not bleed excessively. The authors report identical reductions in total postoperative transfusions with epsilon-aminocaproic acid (61% reduction versus placebo) and high-dose aprotinin (62% reduction). In these studies, the data from the aprotinin-treated patients involve a series of repeat sternotomy, valvular surgeries, and additional complex patients compared to the small number of EACA treated primary CABG surgery patients. Although both drugs reduced rates of reexploration to similar degrees, this effect was statistically significant only with high-dose aprotinin. Finally, most of the methods used to study the incidence of adverse events in the EACA-treated patients do not conform to the rigorous evaluation of FDA sponsored clinical studies to evaluate safety issues with aprotinin.

A meta-analysis study by Fremes et al. (86) reviewed 33 randomized placebo-controlled trials involving DDAVP, EACA, tranexamic acid, and aprotinin. All were published before June 1993 (therefore not including several large aprotinin trials published in 1994). The authors implied that the meta-analysis supports the prophylactic use of EACA, tranexamic acid, or preferably aprotinin rather than desmopressin for reducing postoperative bleeding associated with an open heart operation and the limitation of allogeneic blood use where indicated.

Aprotinin and epsilon-aminocaproic acid are routinely used to reduce bleeding during cardiac surgery. The marked difference in average wholesale cost between these two drug therapies (aprotinin, $1,080 versus epsilon-aminocaproic acid, $11) has caused significant controversy regarding their relative efficacies and costs. Bennett-Guerrero (87) reported a multicenter, randomized, prospective, blinded trial, patients having repeated cardiac surgery received either a high-dose regimen of aprotinin (total dose, 6×10^6 kallikrein inactivator units) or epsilon-aminocaproic acid (total dose, 270 mg per kg). Two hundred four patients were studied. Overall (data are median (25th to 75th percentiles)), aprotinin-treated patients had less postoperative thoracic drainage (511 ml (383 to 805 ml) versus 655 ml (464 to 1,045 ml); $P = 0.016$) and received fewer platelet transfusions (0 (range, 0 to 1) versus 1 (range, 0 to 2); $P = 0.036$). The surgical field was more likely to be considered free of bleeding in aprotinin-treated patients (44% versus 26%; $P = 0.012$). No differences, however, were seen in allogeneic erythrocyte transfusions or in the time needed for chest closure. Overall, direct and indirect bleeding-related costs were greater in aprotinin-treated than in epsilon-aminocaproic acid-treated patients ($1,813 ($1,476 to 2,605) versus $1,088 (range, $511-2,057); $P = 0.0001$). This difference in cost per case varied in magnitude among sites but not in direction. The authors concluded that aprotinin was more effective than epsilon-aminocaproic acid at decreasing bleeding and platelet transfusions. Epsilon-aminocaproic acid, however, was the more cost-effective therapy over a broad range of estimates for bleeding-related costs in patients undergoing repeated cardiac surgery. A cost-benefit analysis using the lower cost of half-dose aprotinin ($540) still resulted in a significant cost advantage using epsilon-aminocaproic therapy ($P = 0.022$).

Recombinant Coagulation Products

Coagulation products used to manage bleeding in patients with hemophilia, von Willebrand's disease (vWD), or acquired inhibitors to antihemophilic factor include AHF concentrates, factor IX concentrates, factor VIIa, and factor IX. (62,87) Although these agents are specifically approved for patients with hematologic disorders, they are also used to manage acute bleeding episodes in patients during cardiac and noncardiac surgery. Currently, the agent most often reported is recombinant activated factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk) that is approved in the treatment of patients with hemophilia with inhibitors who are bleeding, and to facilitate hemostasis in life threatening, refractory bleeding in complex clinical situations (88–91).

Multiple case reports describe the application of rFVIIa for life-threatening and refractory bleeding despite hemostatic factors and platelets in patients with both preexisting and acquired hemostatic disorders, during both cardiac and non cardiac surgery (90–92). Although rFVIIa has been reportedly used to treat a wide variety of coagulation defects, it is currently approved for patients with hemophilia who have inhibitors. Although 90 mcg per kg is usually the initial starting dose in patients with hemophilia, lower doses of 30 to 45 mcg per kg have been reported in surgical patients to be effective. Additional studies are needed to further evaluate dosing, safety and efficacy in perioperative use of rFVIIa.

SUMMARY

Hemostatic agents improve hemostasis by multiple mechanisms that include improving primary hemostasis, stimulating thrombin generation/fibrin formation, or inhibiting fibrinolysis. Although hemostatic factors are mainstays of therapy, pharmacological agents are important adjuncts as blood products become increasingly in short supply, newer longer acting anticoagulants and platelet inhibitors are increasingly being used, and alternative therapies need to be considered for refractory bleeding when prophylactic therapy is not possible. Aprotinin has been extensively studied for prophylactic administration, with both safety and efficacy. Lysine analog fibrinolytic inhibitors also have been extensively studied, with TA demonstrated to be effective. However, there is a paucity of safety data involving these agents. DDAVP increases VWF, and is often used as a hemostatic agent with little data demonstrating efficacy, especially for the treatment of bleeding in surgical patients. Because coagulation in vivo proceeds by the tissue factor/factor VII(a) pathway, recombinant factor VIIa has been developed as a prohemostatic agent with multiple reports suggesting its efficacy for refractory life threatening hemorrhage in uncontrolled clinical studies with severe and complicated coagulation defects. At present, a more general use of this agent for bleeding patients without an apparent coagulation defect is the subject of current clinical trials.

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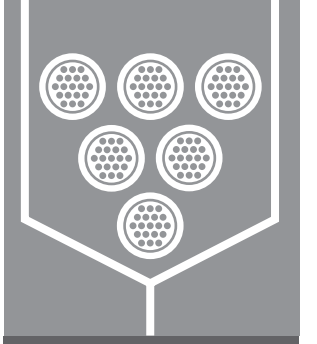

31

Fibrin Glue and Platelet Gel

Bruce Searles *Cody Trowbridge*

One of the blood's most fundamental responsibilities is to provide hemostasis for the body. Toward this goal it as been endowed with a multitude of specialized proteins and cells which cooperate effectively through redundant biochemical pathways to engineer complex biological matrices (coagulum) which prevent blood loss and stimulate wound healing before strategically disassembling (fibrinolysis). The coagulation cascade is a bioamplification system which culminates with the collaborative interaction between a developing fibin polymer matrix and activated platelets. Thrombin, the activated product of prothrombin (factor II), is the enzyme primarily responsible for both fibrinogen (factor I) and platelet activation. In vivo the development of a coagulum involves participation of both fibrin and platelets at normal physiologic concentrations. However, through modern blood separation and concentration technologies, the properties of each of these components can be individually exploited to provide a vascular sealant which is topically applied at the injury site and provides supraphysiologic hemostatic and wound healing abilities. The purpose of this chapter is to review the pertinent biochemical mechanism of action responsible for the beneficial effects of fibrin glue and platelet gel and describe the current state of the art for each of these products (Figure 31.1).

FIBRIN GLUE

Development and Resorption of a Fibrin Matrix

Thrombin is the activated enzyme of prothrombin, a plasma glycoprotein with a molecular weight of 72,000 (1). Thrombin plays a number of divergent rolls in hemostasis by supporting fibrinolysis as well as coagulation and additionally stimulating cascades which promote tissue repair (2). Most relevant to this discussion is thrombin's role in supporting coagulation which it does by promoting the development of a fibrin clot and by stimulating platelet aggregation (thrombin's effect on platelets will be discussed in greater detail later in this chapter). Thrombin converts fibrinogen, one of the most abundant proteins in plasma, from its functionally inert form into its activated form, fibrin. Fibrinogen, has a molecular weight of 340,000 and is composed of three pairs of polypeptide chains called Alpha, (α), Beta, (β), and Gamma, (γ) (1). By cleaving first an A segment from each chain in the α pair and then a B segment from each chain in the β pair, thrombin converts fibrinogen to its soluble fibrin monomer form which is capable of spontaneously organizing into a matrix through weak side-to-side and end-to-end hydrogen bonding between monomers (2). Additionally, thrombin converts calcium (Ca^{++}) bound factor XIII from its inactive form, consisting or 2α and 2β chains with a combined molecular weight of 320,000, to its activated form, XIIIa, which is a 4,500 molecular weight peptide cleaved from the α chain (1). Factor XIIIa, in the presence of Ca^{++} serves to stabilize the spontaneously organized fibrin mesh by introducing strong covalent bonds within the weakly associated fibrin polymer matrix (2).

Fibrinolysis, the systematic disassembly of the fibrin matrix, is initiated simultaneously with the development of a fibrin clot. The primary mediator of fibrinolysis is plasmin, the 85 Kd fragment of the inactive single chain glycoprotein, plasminogen (1). Plasminogen may circulate freely in plasma but is predominantly bound to fibrinogen. Fibrin-bound plasmin dissolves the fibrin matrix through repetitive cleavages of the α, β, and γ chains, producing first

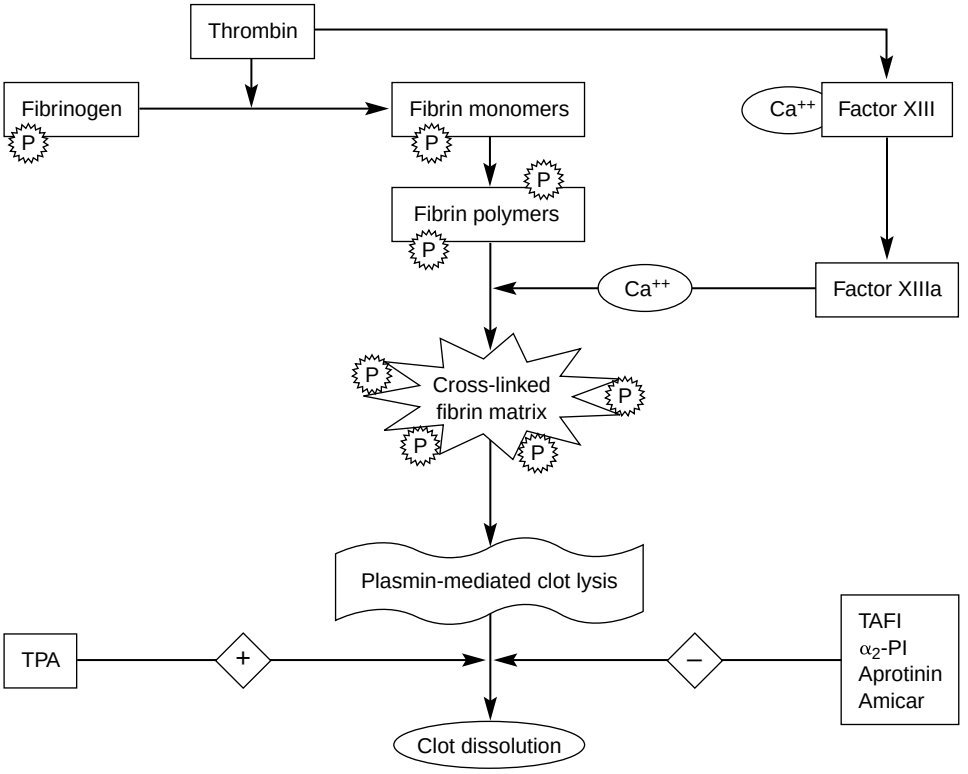

Figure 31.1 Coagulation and fibrinolytic steps relevant to fibrin glue.

an *X monomer* which is further degraded to a *Y fragment* which is also further degraded to *D* and *E fragments* (2). Plasmin-mediated clot lysis is largely regulated through the combined effects of a variety of endogenous plasminogen activators and plasmin inhibitors and can be moderated through exogenous pharmacologic agents employing varying mechanism (Figure 31.2).

Introduction to Fibrin Glue

Fibrin glue (aka: fibrin sealant, fibrin gel, fibrin tissue adhesive) is a topical hemostatic product which consists minimally of three primary ingredients, thrombin, calcium chloride and fibrinogen, and generally includes a combination of secondary ingredients including, Factor XIII and an

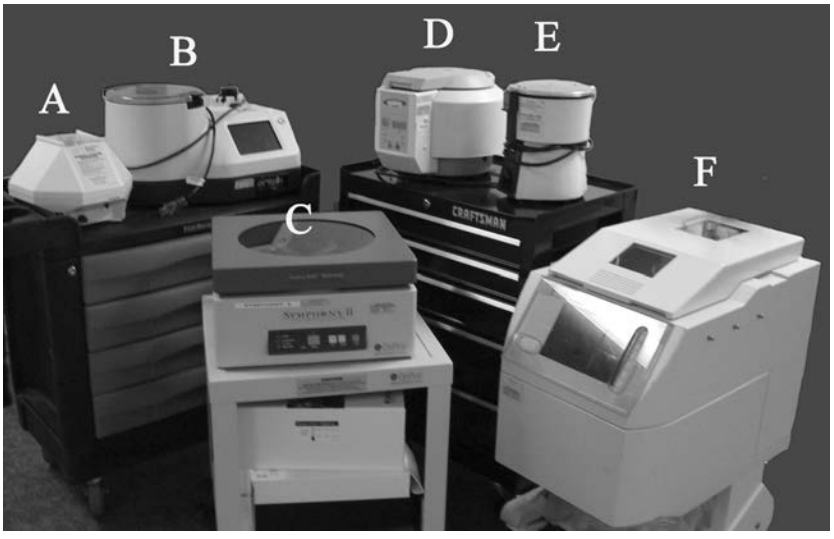

Figure 31.2 Examples of platelet gel devices. A: MTF Cascade; B: Cobe Angel; C: Harvest Symphony II; D: Biomet GPS; E: Simple Tube Centrifuge; F: Terumo Continuous Autotrans fusion System.

antifibrinolytic agent (3). It can be produced in-house by the hospital blood bank from autologus or homologus sources of fibrinogen. Additionally, several manufacturers worldwide offer commercially prepared fibrin glue products which can be reconstituted and applied with minimal delay. Fibrin glue is widely recognized for its hemostatic an adhesive properties but may also support wound healing to a lesser degree.

Components of Fibrin Glue

Thrombin

Thrombin is responsible for converting fibrinogen to fibrin monomers which develop into an insoluble clot. It is generally reported that the concentration of thrombin in a fibrin gel product influences the rate of clot formation. Consequently, glues with lower thrombin concentrations will gel slower than glues with higher thrombin concentrations. Based on this, glues with lower thrombin concentrations are more aptly suited for surgeries where tissue repositioning may be necessary (skin grafting) and glues with higher thrombin concentrations are more appropriate for surgeries where quick hemostasis is required (cardiovascular and gastrointestinal) (3). However, it has been reported that the clot rate remains constant at thrombin values from 20 to 1,000 IU per ml (4). Interestingly, there are no commercially prepared fibrin glue products with thrombin concentrations below 200 IU per ml

Fibrinogen and Factor XIII

Fibrinogen is converted to fibrin by thrombin and serves as the primary structural unit of the developing clot. Factor XIII increases the strength of a clot as much as fivefold (5). It is generally reported that the fibrinogen concentration of the fibrin glue product directly influences the strength of the clot, (6) however it has also been reported that the strength and adhesive property of the clot is maximized at fibrinogen values of 40 mg per ml, and that higher fibrinogen levels did not produce stronger or more adherent clots (4).

Calcium Chloride

Ionized calcium is involved in factor XIII activity. Calcium chloride solution is used as a source of calcium ions for most fibrin glue products. It is generally used to reconstitute the thrombin in commercial products and in-house preparations that use lypholized thrombin (3).

Antifibrinolytic Agents

Plasminogen is highly associated with fibrin and once activated cleaves fibrin polymers dissolving the clot. The activity of plasmin is greatly influenced by the local tissue environment. Antifibrinolytic and hemostatic agents such as Aprotinin, tranexamic acid, or ϵ-aminocaproic acid are often included in a fibrin glue preparation to help stabilize the clot, by inhibiting the activity of plasmin and improving the late lifespan of the clot (3,7). The most common of these agents is Aprotinin that is prepared from bovine tissue and has been associated with hypersensitivity reactions. While hypersensitivity reactions to aprotinin are rare, (0.5 per 100,000 for all reactions) there have been published reports of immediate allergic reactions in adults and children to the Aprotinin included in fibrin glues (8–10). Consequently, its inclusion in fibrin glue product has been questioned and new fibrin glues are being developed which do not include Aprotinin (11).

Fibrin Glue Products

In-house Fibrin Glue Preparations

For decades, the fibrinogen source for fibrin glue was processed in-house from either autologus plasma or cryoprecipitate from single or pooled human donors. Commercially prepared fibrin glue products have been available in Europe since the late 1970s but did not receive Food and Drug Administration approval for sale in the United States until 1998 (3). Additionally new devices and recombinant protein technology hold promise for a new generation of fibrin glue products in the future.

There are limitations associated with each of the currently available fibrin glue products. Preparing autologus fibrinogen typically is an expensive and time-consuming process requiring predonation days in advance of the surgery. The cost and inconvenience are particularly concerning for the patients that predonate whole blood and subsequently do not require fibrin glue during the course of their surgery. Furthermore not all patients will qualify for predonation.

Fibrinogen produced in-house from single and pooled donor units has all of the obvious issues related to transmission of blood-borne disease (12). There is one documented case of HIV-1 transmission from an in-house preparation of fibrin glue (13). The quality and purity of all in-house fibrinogen preparations is also a matter of debate. Perhaps the greatest limitation of the in-house prepartions is the source of thrombin used to activate the fibrinogen. Commercially prepared bovine thrombin may contain bovine factor V as an unregulated impurity (6). There are numerous reports in the literature describing the development antibodies to bovine thrombin and bovine factor V which lead to prolonged coagulopathy following surgery (14–17).

Commercially Prepared Fibrin Glue Products

Commercially prepared fibrin glue products are different from in-house preparations in a number of ways including:

viral inactivation of the human blood components, use of human thrombin as an activator, consistency/quality control of the product and storage/preparation of the product. Concerns regarding blood-borne disease transmission are markedly reduced as the human blood components are procured from donors subjected to a rigorous screening process and the products undergo procedures to inactivate viruses (18). There have been no documented cases of disease transmission as a result commercially prepared virus inactivated fibrin glue product (14). In addition to the virus inactivated human fibrinogen, virus inactivated human thrombin from pooled donors is used as an activator in commercially produced fibrin glue products. The use of human thrombin reduces the immunologic risks of the patients that were associated with the use of bovine thrombin. The consistency and quality of commercially prepared products is far more standardized than that of product produced in-house. Table 31.1 describes the components of all the commercially available fibrin glue products as of 2003.

Commercial fibrin glue products are either supplied in freeze-dried form or as frozen solutions. Lypholyzed componets (thrombin and fibrinogen powders are provided in separate vials) are generally stored in a refrigerator 2°C to 8°C and warmed to room temperature prior to reconstitution. Once reconstituted the individual components are stable at room temperature for up to 24 hours. Products supplied as frozen solutions are stored in standard a standard freezer at or below –18°C and are thawed prior to use (19). Dickneite et al. (20) evaluated 12 commercially available fibrin glue products for adhesive strength, and hemostasis efficacy and graded their performance as good, fair or poor (Table 31.2). In general the majority of all commercial products tested achieved either a good or fair ranking in these standardized tests (20).

Devices for Rapidly Producing Autologus Fibrin Glue

The current state of the art for fibrin glue products is already in clinical us in the United Kingdom. The CryoSeal FS system (Thermogenesis Corp. Rancho Cordova, Calif) is a blood component separation device which is capable of separating and concentrating thrombin and cryoprecipitate (as the source of concentrated fibrinogen) from a single unit of autologus blood. The separated components are then sterilely aliquoted and individual transfered into dual syringe administration sets which can be stored for up to 60 days at −20°C. One center in Italy has reported on their use of the CryoSeal FS system. The quality control values of their study group (n = 30 patients) revealed fibrinogen concentrations of 36±12 mg per ml, thrombin

TABLE 31.1
COMPOSITION OF FIBRIN SEALANTS

		Human Fibrinogen (mg/mL)	Human Factor XIII (U/mL)	Human Thrombin (IU/mL)	Bovine Aprotinin (KIU/mL)
Tisseel (Tissucol) Duo Baxter-Immuno AG (Austria)	Frozen solution	70–110	10–50	500	3000
Tisseel (Tissucol) Kit Baxter-Immuno AG (Austria)	Lyophilisate	70–110	10–50	500 and 4	3,000
Tisseel VH Kit Baxter-Immuno AG (USA)	Lyophilisate	75–115	Activity not known	500	3,000
BeriplastP Aventis Behring (Germany)	Lyophilisate	90 (65–115)	60 (40–80)	500 (400–600)	1,000
Hemaseel APR Haemacure (Canada) (as Tisseel VH Kit Baxter-Immuno)	Lyophilisate	75–115		500	3,000
Quixil R Omrix Biopharmaceuticals SA (Israel)	Frozen solution	40–60	None	900–1,100	None (tranexamic acid 92 mg/mL)
Crosseal Omrix Biopharmaceuticals SA (Israel)	Frozen solution	40–60	None	800–1,200	None tranexamic acid
Bolheal Kaketsuken Pharmaceutical (Japan)	Lyophilisate	80	75	250	1,000
Biocol LFB- Lille (France)	Lyophilisate	127	11	558	3,000
VIGuard F.S. Vitex: VI Technologies (USA)	Lyophilisate	50–95	3–5	200	None

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TABLE 31.2

PERFORMANCE OF 12 COMMERCIALLY AVAILABLE FIBRIN GLUE PRODUCTS IN STANDARDIZED PARTIAL LIVER AND KIDNEY MODELS USED TO ASSESS HEMOSTATIC EFFICACY AND A NOVEL PIG SKIN MODEL TO MEASURE ADHESIVE CLOT STRENGTH

	Adhesive Strength in Vitro	In Vivo Efficacy (Hemostasis)		Device (Spray Characteristics) Homogeneous+Focused Application Distribution and Size	Drop
		Early	Late		
A: Beriplast P	+++	+++	+++	Spray Tip+++, Berijet+++	Spray tip:+++, Berijet:+++
B1: Tissucol Kit	+	+++	+++	Duploject spray set:+++	Duploject spray set:+++
B3: Tisseel VH Kit	+	+++	++	Duoflo:+++	Duoflo:+++
C: Biocol	+++	+	n.t.	Necesta device:+	Necesta device:+
D: Bolheal	+++	+	+++	Bolheal device:+++	Bolheal device:+++
E: Hemaseel APR		++	n.t.	Fibri Jet:+ Hema Myst:+	Fibri Jet:+ Hema Myst: +
F: Quixil	+++	+	+	Mixjet:+++	Mixjet:+++
G: Greenplast	+++	++	n.t.	No spray device	No spray device
H: Beta Guangzhu	+++	+++	n.t.	Spray tip:+++	Spray tip:+

n.t., not tested; (+) poor; (++) fair, (+++) good.
Hemaseel FibriJet, dual spray tip; Hemaseel HemaMyst, old device since replaced by a new HemaMyst aerosol device.
(Reprinted with permission of BC Decker. Adapted from Dickneite G, Metzner H, Pfeifer T, et al. A comparison of fibrin sealants in relation to their in vitro and in vivo properties. *Thromb Res.* 2003;112:73–82.)

activity 40±2 IU per ml and factor XIII concentrations of >6 IU per ml (21). While these concentrations are below the concentration found in commercially prepared products, they are above the experimentally derived minimum concentrations for an effective glue (4).

The Future of Fibrin Glue: Recombinant Proteins

The next evolutionary step for the development of fibrin glue will the application of recombinant fibrin and thrombin. One company (Pharming Group, Nev) has developed an experimental recombinant fibrin which has is being evaluated for efficacy as a tissue sealant by the United States Army.

Applications of Fibrin Glue

Fibrin glue has been reported to: reduce the need for surgical drains and pressure bandages in cosmetic facial surgery, (22) improve hemostasis and graft take of skin grafts, (23) reduce blood loss, (24) especially in anticoagulated patients, (25) and patients with preoperative bleeding disorders (26–28), facilitate sutureless corneal and conjunctival surgery, (29) facilitate osteochondral fracture fixation of the digits, (30) to name just a few. In fact, a review of the literature for the therapeutic uses of fibrin adhesives quickly reveals that practically every surgical specialty has reported on their use and experience with fibrin glue. Numerous review articles have been published which discuss the findings of dozens of individual papers for variety of surgical disciplines (19,23,29,31–37). In general the shortcoming of this body of the literature is that few randomized prospective studies have been done to establish the benefits of fibrin glue applications. The majority of the reports are based on a continuous series of patients and results of specific surgeons or institutions. These reports generally conclude that the use of fibrin glue has improved the outcomes in their series of patients.

Traditionally, fibrin glue products prepared in-house have been administered through a two syringe technique directly onto the wound where the mixing of the components will occur directly on the tissue. Alternatively some clinicians connected the two syringes to a stop cock or a dual lumen catheter for greater control. Most commercial fibrin glue manufacturers recommend a special applicator which controls the mixing and generates uniform output ranging from a stream of activated fibrinogen to a fine spray or an aerosol. Another application technique which has been productive is the application of fibrin glue through a long catheter or an endoscope to treat tissues that are hard to reach or to facilitate a minimally invasive approach to the patients care. Unfortunately, some highly viscous commercial preparations can be difficult to administer through long catheters.

Emerging Applications of Fibrin Glue

Another exciting application of fibrin glue has less to do with its hemostatic or adhesive properties and more to do with its function as a biodegradable scaffold which can be impregnated with drugs or other therapeutic agents or cells. Researchers have used fibrin glue to provide targeted

delivery of antibiotics, stem cells, autologus cartilage, and Calcium phosphate bioceramic granules used for bone reconstruction (38–41). It is expected that this application of fibrin glue will continue to expand.

Contraindications

With regard to the prescribing information provided with the commercial products available in the United States, Tisseel is contraindicated in patients with known sensativites to bovine proteins (Tisseel prescribing information, Baxter, Westlake Village, Calif). Additionally Crosseal should not be used in contact with CSF or dura mater (Crosseal prescribing information, Omrix biopharmaceuticals Ltd. Kiryat Ono, Israel).

PLATELET GEL

Mechanism of Platelet Activation and Granule Release

While the primary source of platelet activation in vivo is generally considered to be chemical stimulation from injured endothelial cells and contact with the collagen surface of the basement membrane, platelet gel utilizes another equally important pathway. As in the formation of fibrin glue, the initial step in the cascade from platelet concentrate to platelet gel is stimulation by the proteolytic enzyme thrombin. Thrombin first binds to the G-protien GPIb which stimulates rearrangement of the actin cytoskeleton and facilitates the cleavage of protease activated receptors (PAR-1, and PAR-4) on the surface of the platelet. Within seconds the intracellular calcium concentration of the platelet increases 10-fold triggering platelet aggregation and the secretion of the contents of the granules and dense bodies, releasing through exocytosis, a milieu of substances including adhesive proteins, growth modulators and coagulation factors as well as additional agonists of platelet stimulation (1).

Introduction to Platelet Gel

The evidence supporting the application of platelet rich plasma as a gel is rapidly accumulating, but is currently limited to primarily small case series, case reports, and few randomized controlled trials. However, the physiological basis for this application is compelling and the early results are promising. Further, the potential applications are widespread in medicine, encompassing soft tissue injury (surgical or otherwise), bone regeneration, and chronic wounds. While speculative, the use of platelet rich plasma as a gel may ultimately be established as the most efficacious autologous blood component therapy, given the mixed results of predonation, intraoperative pheresis, and acute normovolemic hemodilution.

Platelet gel is simply the application of autologous platelet rich plasma (PRP) combined with $CaCl_2$ (to reverse the citrate used as an anticoagulant) and thrombin (either autologous or bovine). Thrombin, as the most powerful platelet agonist known, is used to rapidly activate the captured platelets to ensure both adhesion and release of alpha granule contents. The release of the contents of the alpha granules has been the topic of considerable interest, as they contain over 40 identified growth factors and a multitude of other bioactive substances. These cytokines have demonstrated a range of activities, from cell migration, proliferation and differentiation to angiogenesis (42–44). The theory behind many applications of platelet gel center around the release of these growth factors. A high concentration of platelets, preserved until application at the site of injury, should release a super physiological level of platelet contained growth factors. High levels of these growth factors may result in expedited healing, especially in the early phases of tissue regeneration (cell migration, differentiation, angiogenesis). In the few randomized controlled trials to date, these effects have resulted in decreased pain and expedited sternal healing postcardiac surgery, improved anatomical success of macular hole surgery, and decreased edema and ecchymosis after deep-plane rhytidectomy (45–47). Lower levels of evidence suggest that platelet gel improves the osteoinductive properties of bone grafts with shortened ingrowth time, and shortened healing time and hospital stays with soft tissue wounds (48,49).

The considerable interest in growth factor therapies prompted the development of recombinant platelet derived growth factors, which have been used clinically with some success (50–52). However, these preparations contain only a single growth factor, whereas platelet gels contain several. Further, the platelets contain other substances that may prove beneficial, including known vasoactive agents and series of thrombin releasable antimicrobial peptides (53). The latter agents may work in concert with leukocytes, which are also present in large concentrations in platelet gel, to reduce the potential for infection. Although reducing infection is often considered a hypothetical benefit, we reported a significant decrease in sternal infections (both superficial and deep) when platelet gel was applied post cardiotomy in a series of 2,200 patients (54). Other groups have not studied infection as an end point, reporting infection rates only to verify that platelet gel does not cause infection. The inclusion of white cells, however, also increases growth factor delivery as they produce similar as well as unique bioactive substances (55). Further benefits of

autologous platelet gel include the ability to be derived from an autologous source, to be prepared from recently donated blood at the point of care, and can be obtained from a renewable source (the patient). However, unlike platelet gel, the recombinant growth factors are produced within strict FDA guidelines and have a known level of potency.

Although platelet gel has been reported as a component of topical hemostatic agents to reinforce the glue and provide cytokine content, platelet gel is not used in this role as a stand-alone agent (56,57). Due to the methods of preparation, the platelet rich plasma used for platelet gel contains a high concentration of platelets and white blood cells, but fibrinogen levels remain at native concentrations (58). However, adequate fibrinogen levels are essential for clot strength, and topical hemostatic agents require higher than native levels (59,60). Platelet gel therefore lacks the tensile strength to prevent bleeding, but the adhesive and sealant properties of the gel are important (61). As a delivery vehicle for growth factor concentrates, platelet gel adhesive properties successfully localize the application by preventing runoff. In applications where platelet gel is used in combination with graft material, the gel serves an important function of consolidating the graft material into a single unit. Fibrin glues, on the other hand, generate the required tensile strength to prevent bleeding, but lack the concentrated level of cytokines, so the primary utility is as a biological sealant.

Preparation of Platelet Gel

The preparation of platelet rich plasma for platelet gel applications has its roots in plasmapheresis. The principles of production are identical—a centrifugal force is applied to separate the components of blood based upon differing specific densities. The traditional buffy coat is the target fraction, containing not only the highest concentration of platelets, but also a high concentration of white cells. The details of the actual separation techniques can be quite divergent, ranging from makeshift uses of existing supplies (tube method), to extended utilization of cell processing machines (autotransfusion), to stand alone bench top devices (PRP specific).

Blood Bank Methods

The use of standard blood bank procedures, such as apheresis or platelet preparation from whole blood (WB), is not frequently employed due to the associated costs and logistical difficulties. However, these methods have been shown to be superior over the simple tube method (62). The platelet enrichment (PRP platelet count/original platelet count) was highest and most consistent when blood bank plasmapheresis is used (5.25; 3.77 to 6.70) compared to WB preparation (46.6; 2.7 to 17.09) and simple tube preparations (4.11; 1.10 to 48.9). However, platelet function and growth factor content (PDGF-AB, PDGF-BB, TGF-β1) was highest with the WB method and lowest with the tube method, a reflection of the improved preservation of platelet function and the high platelet concentration.

Simple Test Tube Method

The tube method was popular with early clinical investigators due to its low cost and availability. The process requires only sterile 10 mL tubes, ACD, and a centrifuge. The blood is collected into the sterile tubes containing ACD and centrifuged for 10 minutes at 1650x G. The supernatant is collected into a second tube and centrifuged for an additional 15 minutes at 730x G. The platelets form a plug at the bottom, and approximately 0.3 mL of the supernatant is used to resuspend the platelets prior to application.

Aside from yielding a lower concentration of platelets and growth factors, the tube method is limited in flexibility. Capturing a small amount of RBCs at the buffy coat interface to increase the total platelet yield is not possible. Likewise, it is difficult to resuspend the platelet plug in a precise amount of residual plasma, as the amount of supernatant to be removed must be estimated. In addition, the tube method requires several user interventions and multiplies the number of possible exposures to potential contamination.

Autotransfusion Methods

A third and more widely utilized method for the preparation of PRP for platelet gel utilizes autotransfusion devices. The benefit of using these devices is a relatively low cost. Providing the device is already going to be used to salvage and wash shed blood, inexpensive disposable add-ons can be used for plasmapheresis. Unfortunately, these devices typically require larger amounts of blood (250 to 500 mL) when compared to the tube method and the dedicated bench top units. Further, only one utilizes a continuous flow mechanism reminiscent of blood bank plasmapheresis, while the remainders utilize a discontinuous flow mechanism (63). Unfortunately, the tube method has not been compared to the autotransfusion method, but autotransfusion methods have been compared to blood bank methods in intramanufacturer studies, between different autotransfusion devices, and with bench top devices (64–66). The available data comparing autotransfusion to blood bank methods is primarily limited to comparing stored platelets with autologous intraoperative derived platelets and therefore has little relevance to the application of platelet gel. However, the continuous flow device has compared favorably with the dedicated bench top devices, but the discontinuous flow devices are inferior in terms of platelet yield and growth factor concentrations (65,66). The continuous flow autotransfusion device is

used at our institution when both autotransfusion and platelet gel are requested. However, if a central venous line is not available, or if the patient cannot tolerate the removal of 400 to 500 mL blood (i.e., aortic stenosis, LV dysfunction, or severe coronary artery disease in noncardiac surgery) a smaller volume device is used.

Alternative technologies are available to further concentrate the platelets contained in the PRP fraction. The process resembles ultrafiltration in that the PRP is passed through hollow fibers, and hydrostatic pressure gradients are used to remove additional free water. Unfortunately, the process is a strong stimulant of platelet activation, and the resulting growth factor concentrations suggest that premature activation occurs at a high rate (61).

Dedicated Platelet Gel Devices

As novel indications and more compelling supportive data continue to evolve, new devices continue to emerge to harvest platelet rich plasma specifically for the production of platelet gel. These devices generally offer more flexibility and require the removal of less volume (20 mL to 180 mL) than the autotransfusion devices. The dedicated bench top devices also require fewer user interventions than the simple tube method, thus limiting potential contamination and user dependent variability in product quality. The trade-off for these benefits is increased cost.

The bench top devices have been compared between similar devices as well as with the autotransfusion devices, but not with the tube method or blood bank methods. In general, the continuous flow autotransfusion device compares favorably with the best bench top devices, but the discontinuous flow autotransfusion devices perform the worst in terms of platelet concentrations and growth factor content (65,66). Not all of the bench top devices performed on an equal basis, and each device offers different capabilities and flexibilities. At one end of the spectrum, some devices require a fixed amount of WB and produce a fixed amount of PRP. Other devices allow the user to determine the amount of blood to be processed, the final volume of PRP, the resulting PRP hematocrit, and alter the processing speeds and times.

General Considerations

Regardless of which method is used to produce platelet gel, or if growth factor delivery, adhesion, or sealant properties are the desired endpoints, several considerations should be taken regarding the handling of the product. All of the methods and all of the potential applications benefit from preserving as many original platelets as possible. Platelet concentration is important, but functional capacity of the applied platelets is essential. Therefore, every effort should be taken to avoid prematurely activating the platelets and to promote preservation until application.

The first step in the production of platelet gel is the removal of an aliquot of WB from the patient. The phlebotomy should be performed prior to incision, and preferably prior to the induction of anesthesia. Some evidence suggests that a central venous line is the preferred site for withdrawal (67). More importantly, the largest bore catheter available, or applicable, should be used and the blood should be withdrawn slowly to avoid the generation of excessive negative pressures. If an indwelling line is used, care should be taken to remove a sufficient amount of waste to ensure all flush/IV fluid is removed prior to withdrawal. If the procedure is a standard phlebotomy, remove at least 3 mL of waste to eliminate the presence of any residual tissue factor. Heparin should not be used as the anticoagulant, and CPD should be avoided. Instead, ACD should be used for point of care harvest of platelets as it is reversible with calcium and does not contain aggregation-promoting phosphates (68).

Controversy exists concerning patients receiving platelet inhibitor therapy and how this may impact the application of platelet gel. Some believe that the platelet gel process would be rendered ineffective by platelet inhibition, while others believe that platelet inhibition would be helpful. By preventing the premature activation of platelets during withdrawal, processing, and temporary storage, the presence of platelet inhibitors may result in the preservation of a greater proportion of the harvested platelets. Upon application, the powerful platelet agonist properties of thrombin would be able to overcome the inhibition. Thus, platelet inhibitors may be able to prevent the undesirable premature activation of the platelets. Data concerning platelet inhibition is limited to a single in vitro study of whole blood using prostaglandin E1, aspirin, and apyrase as experimental inhibitors. When comparing the primary endpoints (concentration of PDGF and TGF-ß1), the authors found a mean of 400% greater growth factor concentration in the presence of platelet inhibition, suggesting that platelet preservation prior to application may be a beneficial effect of these therapies (69).

Some authors have suggested that methods that reduce user intervention are desirable, as this limits the potential for contamination of the product (66). More important, careful adherence to the principles of sterile technique should be employed during phlebotomy, processing, temporary storage, and delivery of the platelet gel to avoid the potential for contamination (Table 31.3).

Application of Platelet Gel

Clinical conditions in which platelet gel has been applied include chronic skin ulcers (i.e., diabetic, ischemic); bone

TABLE 31.3
PLATELET GEL PRODUCTION METHODS

Method	Volume Required	User Interventions	Product Volume
Simple tube	2–60 mL	High	Variable
Autotransfusion			
Discontinuous	300–500 mL	Medium	100 mL
Continuous	250–500 mL	Medium	100 mL
Dedicated device			
SmartPRep2	20–120 mL	Low	5–20 mL
Magellan	60–180 mL	Low	5–30 mL
Angel	60–180 mL	Low	User defined
GPS	60 mL	Low	5 mL
Cascade	9 mL	Medium	Solid mass

SmartPReP2, Harvest Technologies. Magellan, Medtronic. Angel, Cobe Cardiovascular. GPS, Biomet. Cascade, Musculoskeletal Technology Foundation.

graft placement in oral maxillofacial, orthopedic surgery; bone integrated implants; oral and nasal fistulas; macular holes and leaking blebs in opthamological surgery; dental surgeries; sternal, arm, leg incisions in cardiac surgery; plastic surgery; cartilage avulsion; and trauma surgery. The list is not inclusive, as it continues to evolve. Essentially, platelet gel has been applied to soft tissue injuries and grafts (tendon, cartilage, skin, and muscle), chronic non-healing wounds, and grafts to bone. The potential applications are ubiquitous in medicine, although few have received intense investigative scrutiny. Fortunately, the applications can be broadly separated into two categories: topical or as a graft component. Generally, the PRP is applied in a 10:1 ratio, 10 parts of PRP to one part thrombin/$CaCl_2$. When bovine thrombin is used, 5,000 units are usually reconstituted in 5 mL10% $CaCl_2$.

While platelet gel can be applied topically to bone, most topical applications are to soft tissue. The application can be simple and straightforward: with a 10 mL syringe of PRP in one hand and a 1 mL syringe of Thrombin/ $CaCl_2$ in the other, the two can be applied to the surface by concurrent depression of the plungers. A variety of applicators and tips are available, however, to aid the process. The utilization of these kits allows more precise mixing and the ability to apply the gel to difficult to reach locations. For example, platelet gel can be applied to the tunnel used for endoscopic saphenous vein harvest for aortocoronary bypass grafting by using a long, flexible tip inserted into the tunnel and slowly pulling back while applying the gel. Alternatively, the gel can be applied as a mist to *paint* larger surfaces with an even coat of gel. Some tips are available to aerosolize the mist via the incorporation of compressed air.

Port access surgeries can utilize the existing surgical instruments as delivery devices. For example, during arthroscopic shoulder reduction, a four-way stopcock can be attached to the scope port and the platelet gel can be applied through the port to the site of reduction. Likewise, platelet gel can be applied as an injection therapy (similar to steroid injections) to tendon, ligament, and cartilage injuries such as tarsal tunnel syndrome. In chronic wounds, the gel is generally applied as a mist, covering the wound with special attention given to the margins. The application occurs after any required debridement and immediately prior to the application of the dressing.

As mentioned, platelet gel can be used as a component of graft material, most commonly bone grafts. While the gel may be most effective in potentiating the regeneration of bone from autologous graft material, it may also be helpful when mixed with cancellous bone. Again, a variety of maneuvers can be used to formulate the graft. The simplest method is to mix the gel with the graft material manually and apply it to the recipient site. More involved techniques can be used to fine tune the application and custom mold the graft. For example, in posterior spinal fusion surgery, a *log* of bone graft can be constructed using disposable components designed to mix the PRP and thrombin precisely with the graft material, containing autologous, allogeneic, and/or cancellous bone chips. The result is a well formed graft consolidated by the adhesive properties of the gel, containing the high concentrations of platelet and leukocyte derived cytokines.

Quality Control (QC) of Platelet Gel

A current review of the efficacy of platelet gel is impeded by the absence of uniform quality assurance measures. Zimmermann (62) was probably the first to identify the

need for standardizing platelet gel preparation methods and the need for full reporting of the methods and final product analysis. The availability of this information, along with a better understanding of the levels of growth factors required for therapeutic effect, may result in improved therapeutic outcomes and improved efficiency. The authors successfully identify that a major problem in evaluating the results of the current research base is the lack of data concerning the quality of the biological product applied. Specifically, the presence of contaminants, the number of WBCs and platelets, and the functional capacity of the final product are rarely reported. The latter, functional capacity is exceedingly important, as it can be diminished based on the degree of platelet activation resulting from the preparation of the product (62).

The assumption that platelet concentration can accurately predict growth factor concentration in the final product is simplistic and flawed (62,66). The potential for prematurely activating the platelets, resulting in the early release of the alpha granules and growth factors, exists at every stage of the process. The early activation of the platelets results in a loss of growth factor activity. First, the growth factors will no longer be localized at the buffy coat interface; instead they will be evenly distributed in the plasma similar to fibrinogen. Second, the half-lives of the identified growth factors are much shorter than the typical interval between inadvertent activation and final application. Thus, excessive negative pressure during phlebotomy, inappropriate handling during processing, poor storage techniques, and poor preparation techniques may all diminish the quality of the final biological product.

Unfortunately, inexpensive and rapid growth factor assays are not available for the routine quantification of growth factors in clinical practice. When different devices and methods have been evaluated in terms of growth factor concentrations, sensitive and specific immunoassays have been used to measure the levels of PDGF-AB, PDGF-BB, and TGF-β1 (62,66). The assays are time consuming and expensive, and therefore are more applicable to investigation and device comparisons than to routine clinical practice.

The distinction between quality control measures and measures appropriate for investigation are important, even when simple platelet counts are considered. It is not known what level of growth factors, or what concentration of platelets, is required to achieve the desired clinical effect for the range of platelet gel applications. However, a higher concentration of functional platelets is universally desired, and a platelet count of the final product could be considered the bare minimum QC testing procedure in clinical practice. A platelet count alone, however, fails to establish the functional preservation of the captured platelets, so a platelet function assay would be a useful adjunctive test.

For device comparisons, clinical investigations and quality assurance additional testing should be employed. Growth factor concentrations will remain the gold standard for these purposes. Regardless of whether or not growth factor assays are performed, blood cell counting should be performed. While the concentration of WBC and platelets of the final product is important for QC efforts, this measure fails to account for variables known to influence the final value, such as baseline counts, volume processed, and final PRP volume. For these purposes, a baseline count should be used in addition to the final product count. Many authors are proponents of reporting the platelet enrichment factor (PRP count/Baseline count) from this data (62,66).

When evaluating different devices for clinical practice, it is useful to count the WBC and platelets in the baseline, PRP, and the PPP samples to determine the efficiency of the device in capturing the available platelets. For device evaluations, final concentration is less important than the ability of the device to capture a high proportion of the platelets available in the phlebotomized blood. Platelet enrichment factor is useful, but it fails to account for the platelets that are lost in the PPP and RBC fractions. By using the calculations below, it is possible to identify the destination of the original platelets and to measure the relative ability to optimize platelet capture in the PRP fraction. Further, the calculations account for the differential recommended dilution of the PRP product the instructions for use of different devices.

$$\%\,\textbf{Yield}: \frac{[\text{Plt}]\ \text{in PRP} \times \text{PRP Volume}}{[\text{Plt}]\ \text{in anticoagulated WB} \times \text{Volume WB}}$$

$$\%\,\textbf{Lost to PPP}: \frac{[\text{Plt}]\ \text{in PRP} \times \text{PRP Volume}}{[\text{Plt}]\ \text{in anticoagulated WB} \times \text{Volume WB}}$$

$$\%\,\textbf{Lost to RBC}: 100\% - \%\,\text{Yield} - \%\,\text{Lost to PPP}$$

The authors have proposed a method to evaluate both the user and the device's ability to capture functional platelets for platelet gel application in a clinical environment (65). Platelet counts are sent on the WB, PPP, and PRP, which allow the calculation of platelet enrichment factor, % yield, % lost to PPP, and % lost to RBC. To qualitatively and quantitatively account for platelet function preservation, the same samples are run on a Thromboelastograph (Haemoscope, Skokie, Ill). The maximum amplitude (MA) of the PRP sample can reveal loss of platelet function, despite a high platelet enrichment factor, prior to application. Further, the relative difference between the PPP and PRP sample allows for the discrimination between the contribution of platelets and plasmatic factor in the MA of the PRP sample.

Testing for bacterial contamination should be done periodically, with the expected occurrence of 0%. After 5 days of storage, banked platelet concentrates have a contamination rate of approximately 0.2% (70). Within the short time

period typical of platelet gel applications (<6hrs), it is unlikely that positive cultures would be detected. The presence of positive culture, a serious complication, should alert the operator of equipment contamination.

Regulatory Issues and Alternative Sources of Platelets/Growth Factors

The use of platelet gel as a growth factor delivery mechanism is a widely unregulated practice. When autologous PRP is drawn and processed at the bedside, the FDA views the process as the practice of medicine, and is therefore not subject to regulation (71). The current recommendation is that the local institutional review board approves platelet gel protocols, and an investigational new drug application should be submitted to the FDA should commercialization be desired. Only FDA licensed pharmaceutical products need to address growth factor concentration and potency issues, thus autologous platelet gel does not fall under the strict FDA growth factor concentration guidelines.

The recombinant products, however, do fall under the FDA guidelines and are the preferable source of growth factor therapy when an allogeneic source is desired. The risk of disease transmission and other complications from transfusion, while low, is unacceptable based on current data concerning benefit versus potential risks. In addition to serious safety concerns, the use of allogeneic platelets for growth factor delivery raises several ethical issues that are best avoided by using autologous platelets or FDA licensed products. Thus, the licensed recombinant products are recommended when the indication is approved and an autologous source cannot be utilized.

Indications/Contraindications

As a relatively unregulated process, the production of platelet gel has poorly defined indications and contraindications. Novel uses continue to emerge, with reported uses ranging from bone grafting to chronic wounds to opthamological surgery to veterinarian applications.

Most authors list active bacteremia as a contraindication, although this contention has not been tested experimentally. Recent exposure to bovine thrombin or known bovine thrombin antibody titres should preclude its use, with autologous thrombin used as an alternative activator. Patients with preload dependent pathologies such as severe aortic stenosis should be considered relatively contraindicated to the removal of large amounts of blood. At our institution, we continue to use platelet gel despite noncompliant ventricles, severe aortic stenosis, severe coronary artery disease, or anemia. Large volume removal is avoided by the use of the smaller volume dedicated devices, and the procedure has been safely performed on 2,900 patients without compromise due to phlebotomy.

Safety

While there is still debate about the efficacy of platelet gel, the procedure is generally considered to be safe. The utilization of autologous blood, drawn and processed sterilely at the bedside, confers little risk. Attempts should be made to keep the blood at the bedside, and standard blood banking precautions should be employed if it becomes necessary to separate the blood from the location of the patient.

The use of bovine thrombin as a platelet activator, however, adds additional risks which are often under emphasized. Several reports of immune modulated reactions to topical bovine thrombin have been reported, although these have typically been for applications other than platelet gel (72–77). Bovine thrombin antibodies are typically a result of impurities in the preparation, specifically the inclusion of bovine factor V. Most patients exposed to bovine thrombin will develop these antibodies, and severe cross reactivity to native factor V may result (78). The authors reported the occurrence of two such reactions with the use of platelet gel, with an overall occurrence of 0.1% (2 per 1,231 procedures) (79). Both incidents resulted in a severe coagulopathy due to factor V consumption, and one of the patients expired as a result.

Due to concerns about the possible transmission of bovine spongiform encephalopathy, bovine thrombin is generally not available outside of North America. Centers without bovine thrombin have developed methods for producing autologous thrombin from the PPP, and dedicated kits should be available in the U.S. in the future. Autologous thrombin is an attractive alternative to bovine sources, from the prospective of both cost reduction and risk reduction, it is currently not possible to determine the activity of the thrombin at the point of care, and standardization of methods is therefore hampered. The actual activity of autologous thrombin is lower than the bovine preparations, and adjustments need to be made accordingly by either using larger amounts of thrombin or allowing more time for the gel to form.

There currently is no standard method for the preparing autologous thrombin. At our institution, we add 5 mL of PPP, mixed with 1 mL 10% calcium gluconate, to a sterile Red Top Vacutainer. The mixture is allowed to incubate for 15 minutes before a 15 minute centrifugation. The supernatant, which contains the thrombin, is decanted into a sterile container in preparation for the final application.

As methods for preparing autologous thrombin become refined and standardized, potential applications may become more widespread. Instead of solely an activator for platelet

gel applications, autologous thrombin may replace bovine thrombin entirely as a topical hemostatic. Autologous thrombin has already been reported for the successful treatment of both intrasplenic and femoral pseudoaneurysms, but the potential applications encompass the widespread utilization of bovine preparation (80,81).

SUMMARY

In summary both fibrin glue and platelet gel are experiencing an ever expanding role in clinical practice. Commercial fibrin glue products provide a sturdy clot with maximum adhesive properties and are effective at improving hemostasis and fixation in a variety of surgical situations. Platelet gel devices are effective at processing autologus platelet concentrates with a recognized ability to accentuate wound healing. New devices and recombinant protein technologies are already being developed which will usher in the next generation of surgical glues and gels. As clinical utilization of these technologies continues to increase, the greatest impediment to advancements in this field is the shortage of prospectively randomized studies which are able to objectively identify the strengths and weaknesses of the current products and serve as a compass for future research and development.

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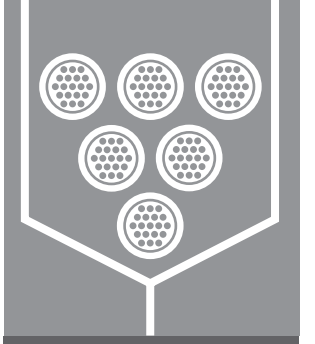
Anesthesia Considerations



Anesthesia Techniques in Blood Conservation

32

Aryeh Shander *Tanuja Rijhwani*

There is a growing body of knowledge suggesting that the anesthetic technique has an influence on surgical outcome. One such area of concern is the influence of anesthetic choice on perioperative blood loss. The focus on blood loss has been heightened during the past decade because of a greater awareness of the risk of transferring infectious agents during allogeneic blood transfusion. As a result, an attempt to evaluate the benefit of techniques, or combination of techniques, to reduce blood loss and the need for transfusion of allogeneic blood products. Historically, anesthetic interventions to decrease blood loss were undertaken to improve operating conditions for the surgeon. What originated as an effort to improve the operative field has, consequently, developed into an area of clinical knowledge aimed at improving surgical outcome.

This chapter focuses on the influence of physiological techniques, such as patient positioning and ventilation mode, controlled hypotension, and the role of regional anesthesia in blood conservation.

PHYSIOLOGICAL TECHNIQUES

Positioning

Proper positioning of a patient for surgery may play an important role in blood conservation. The role of patient position and blood loss is best seen in spinal surgery. Because spinal surgery is most often performed in the prone position, placing the patient with support below the pelvis and shoulders leaves the abdomen free. It has been shown that by preventing pressure on the abdominal wall, the pressure on the vena cava is minimized, thus reducing blood flow through collateral vertebral venous plexuses, known as Batson's plexus (1). The result is a reduction in blood loss. The use of various frames/bolsters has been studied in an attempt to reduce the pressure on the IVC. Bostman et al. (2) showed that blood loss in a frame-supported kneeling position was much less than in the prone position on bolsters. They proposed that the kneeling position lead to a decreased Inferior Vena Cava Pressure (IVCP); however they did not measure IVCP or Intra Abdominal Pressure (IAP). Lee et al. (3) studied changes of IVCP when the same patient was prone on a conventional pad and on a Relton-Hall frame. The authors did not adjust for the type of surgery although different types of surgical patients were studied. No correlation between change in positioning and reduction of blood loss perioperatively could be noted in this study. Park (4) randomized 40 subjects to either the narrow or wide support widths of the Wilson spinal supporting frame. The Wilson frame provides a convenient and stable method of maintaining patients in the flexed position for spinal surgery. The author concluded that IAP and intraoperative blood loss were less in the wide pad support of the Wilson frame. In a correlation analysis between IAP and blood loss, blood loss per vertebra tends to increase with increase in IAP in the narrow pad support width of the Wilson frame.

To assist in minimizing abdominal pressure, it has also been suggested that complete muscle relaxation be maintained (5). An additional technique pertinent to spinal surgery, as well as other surgical procedures, especially those involving the head and neck, (6) is raising the operative site above the level of the heart. Venous return is thereby promoted, reducing blood pooling at the surgical site. The significant risk of venous air embolism, however, must be considered with the latter technique.

Ventilation

During mechanical ventilation, airway pressure increases, resulting in an increase in mean intrathoracic pressure. Because venous return to the thorax is dependent on the difference between peripheral venous pressure and intrathoracic pressure, venous return is, consequently, impeded during inspiratory cycle of mechanical ventilation (7). There is evidence that elevation in intrathoracic pressures during mechanical ventilation raises the peripheral vascular pressure enough to affect blood loss (8–10). Spontaneous ventilation, on the other hand, assists venous return because of reduced mean intrathoracic pressure with inspiration. The hemodynamic differences, therefore, between spontaneous and mechanical ventilation can reduce intraoperative blood loss (8,9).

Another aspect of ventilation affecting venous return is expiratory and inspiratory resistance. Maintaining expiratory resistance as low as possible assists venous return by reducing intrathoracic pressure (11). Appropriate management of reactive airway disease, appropriate setting of the inspiratory-to-expiratory ratio, allowing adequate expiration time, and maintaining unobstructed expiratory flows (e.g., avoiding kinks or buildup of secretions in the endotracheal tube) may be beneficial in reducing blood loss. Interestingly, an inspiratory resistive load that is adapted to an individual patient produces an increase in stroke volume by enhancing venous return and also may be beneficial in blood conservation (11).

PHARMACOLOGICAL TECHNIQUES

Physiology of Blood Loss Reduction During Controlled Hypotension and Regional Anesthesia

In exploring the physiology of controlled hypotension, it is important to determine what aspect of the affected cardiovascular system is responsible for reducing blood loss. Are the beneficial effects of hypotension correlated best with the cardiac output of the heart or the pressure/flow characteristics of the arterial tree and/or venous capacitance system? The question regarding cardiac output was demonstrated by Sivarajan et al. (12). It had previously been suggested that cardiac output correlated with dryness of the surgical field (13). Sivarajan et al. (12) studied 20 subjects undergoing bilateral mandibular osteotomies, randomly assigned to receive trimethaphan or sodium nitroprusside. With no statistical difference in the duration and the extent of mean arterial blood pressure reduction or the total administered intravenous fluids during controlled hypotension (mean arterial pressures of approximately 50 to 60 mm Hg), blood loss between the two groups was the same. When compared with control values for the same group, trimethaphan produced a 37% decrease in cardiac output, whereas sodium nitroprusside produced a 27% increase. Associated with these changes in cardiac output and mean arterial pressure, trimethaphan decreased heart rate, and left total peripheral vascular resistance unchanged, whereas sodium nitroprusside caused a significant rise in heart rate and reduced total peripheral vascular resistance. It is apparent, therefore, that mean arterial pressure correlates with reduced blood loss during controlled hypotension and not reduced cardiac output.

As pointed out by Fahmy, (14) however, the hemodynamic responses to vasodilators such as sodium nitroprusside or trimethaphan depend on ventricular function as defined by the Frank-Starling relationship (Fig. 32.1) and on the effects of the anesthetic agents used. Controlled hypotension with sodium nitroprusside, for example, has been associated with either no change (15,16) or an increase in cardiac output (12). The discrepancies can be explained by the dose response of halothane on cardiac output and baroreceptor reflexes. Halothane not only decreases cardiac output in a dose-dependent fashion (Fig. 32.2) but also attenuates baroreceptor reflexes. Depending on the dosing, therefore, halothane may affect the reflex increase in heart rate produced by sodium nitroprusside (14). Further insight can be gained by looking at the cardiovascular effects of sodium nitroprusside in the awake and halothane-anesthetized states as shown in Figure 32.3.

In a similar fashion, μ-receptor opioids, such as fentanyl, which have central vagal effects, (17) may also offset the

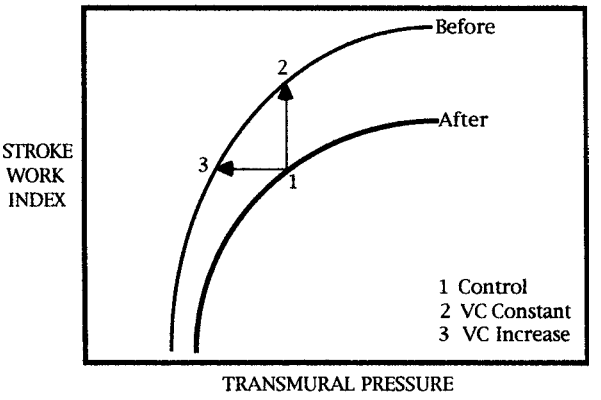


Figure 32.1 Effect of a vasodilator on the Frank-Starling relationship. A decrease in afterload shifts the curve (heavy line) to the left (light line). If transmural pressure (preload) remains constant, the cardiac output will increase; if the decrease in afterload is also associated with a decrease in preload (transmural pressure), then cardiac output will remain constant. VC, venous compliance. (Reprinted by permission from Fahmy NM. Indications and contraindications for deliberate hypotension with a review of its cardiovascular effects. *Int Anesthesiol Clin.* 1979;17:175–187.)

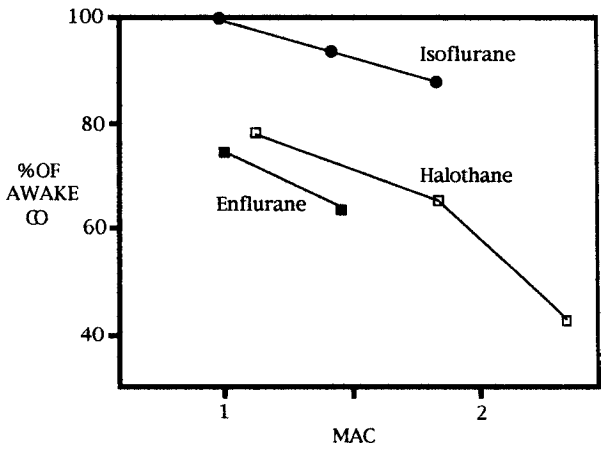


Figure 32.2 Percent change from awake values of cardiac output in anesthetized normocapnic volunteers. CO, cardiac output; MAC, minimum alveolar concentration. (Reprinted by permission from Eger EI. Isoflurane: review. *Anesthesiology.* 1981;55:559.)

reflex increase heart rate of sodium nitroprusside. The resultant cardiac outputs, therefore, will depend not only on the lowered afterload and/or preload caused by the hypotensive agent but also on the changes in heart rate, peripheral vascular hemodynamics, and myocardial effects caused by the dosage and selection of anesthetic agents.

The effect of cardiac output on blood loss has also been evaluated by Sharrock et al. (18) under epidural hypotensive anesthesia. Under equally hypotensive epidural anesthesia with mean arterial pressures of 50 to 60 mm Hg, Sharrock et al. (18) found in 30 patients undergoing total hip arthroplasty and randomly assigned to low-dose epinephrine infusions significantly higher cardiac outputs than those assigned to phenylephrine infusions. Blood loss, however, was not significantly different between groups.

The current available data seem to have established that reduced cardiac output is not associated with reduction in intraoperative blood loss. The other proposed explanations are reductions in arterial and/or venous pressure. Mean arterial pressure, however, is most likely a reflection of hemodynamic change influencing blood loss during surgery (9,18–20). The importance of arterial pressure is demonstrated by Sharrock et al. (19) where intraoperative blood loss was found to be significantly related to the average systolic pressure. In this study, 40 patients undergoing total hip arthroplasty during epidural anesthesia were randomly assigned to two pressure categories: 50 ± or 60 ± 5 mm Hg. Both by quantitative and qualitative measurement, blood loss was significantly greater in the 60 mm Hg group. Blood loss, however, was not significantly related to average intraoperative central venous pressure in the two groups. As pointed out by Sharrock et al. (16,19), although they demonstrated a difference in blood loss with the two degrees of hypotension, the relationship of mean arterial pressure to blood loss is still not entirely clear. Whether the relationship is linear or curvilinear needs yet to be demonstrated.

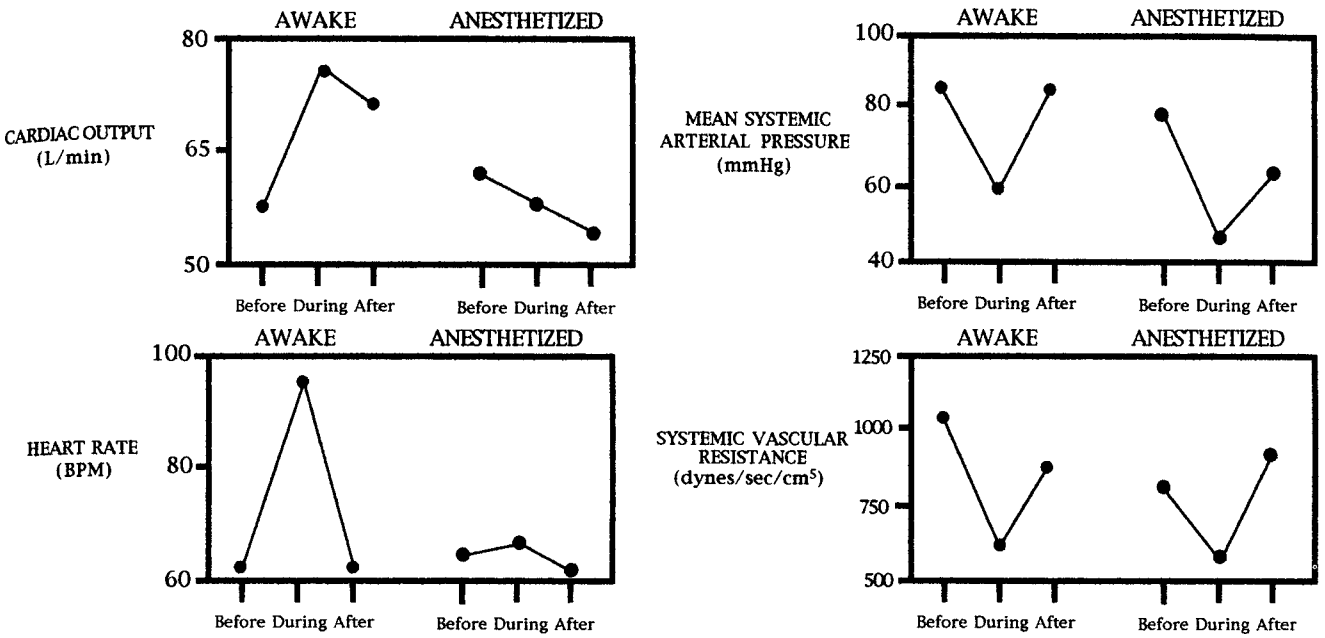


Figure 32.3 Systemic hemodynamic effects of sodium nitroprusside in the awake state and during anesthesia (halothane-oxygen). (Reprinted by permission from Fahmy NM. Indications and contraindications for deliberate hypotension with a review of its cardiovascular effects. *Int Anesthesiol Clin.* 1979;17:175–187.)

The relationship between mean arterial pressure reduction and blood loss is not always consistent. The studies mentioned above involve orthopedic surgery where the best documentation of blood conservation with controlled hypotension has been made due to the extent of blood loss associated with these procedures. Fromme et al. (21) evaluated two levels of hypotension (75 to 85 and 55 to 60 mm Hg) compared with a control group with a mean arterial blood pressure of 90 to 100 mm Hg in orthognathic surgery. No reduction in blood loss at the two levels of hypotension compared with the control group was demonstrated. It is likely, therefore, that other factors, such as type of surgery and positioning, may be more important in determining blood loss in certain types of surgery.

Blood loss during controlled hypotension is at least in part dependent on venous pressure (5,8,19,22). Fahmy (22) studied 91 patients undergoing total hip replacement under general anesthesia who received either nitroglycerine or sodium nitroprusside to induce hypotension. In his study, systolic blood pressures were decreased to comparable levels with the two drugs (73 to 76 mm Hg); mean and diastolic pressures, however, were significantly higher with nitroglycerine (60 to 63 and 52 to 55 mm Hg, respectively) than with sodium nitroprusside (52 to 54 and 42 to 44 mm Hg, respectively). On the other hand, right atrial pressure was significantly lower with nitroglycerin than with sodium nitroprusside, the difference most likely due to the greater dilatation of venous capacitance induced by nitroglycerine (this is simple to explain since NTG is a pure venodialator and NTP is both arterial and venous). Despite the slightly higher mean arterial pressure in the nitroglycerine group, the mean intraoperative blood loss was 578 $\pm$ 82 mL in the nitroglycerine group compared with 762 $\pm$ 93 mL in the sodium nitroprusside group. This difference was statistically significant. In a similar study comparing isoflurane and sodium nitroprusside as hypotensive agents (17) where mean hypotensive arterial pressures and right atrial pressures were comparable, blood loss was the same.

The potential contribution of venous pressure to blood loss can be further understood from studies using epidural anesthesia. Modig et al. (8,9) demonstrated that both intraoperative and postoperative blood loss is significantly lower during epidural anesthesia compared with general anesthesia in patients undergoing total hip replacement. Within their study, two general anesthesia subgroups were also compared: an inhalation (spontaneous ventilation) anesthesia group and an intermittent positive pressure ventilation (IPPV) group. The inhalation anesthesia group had a significantly lower blood loss than the IPPV group. The differences in blood loss are attributed to the greater drop in mean arterial pressure associated with epidural anesthesia and a significant reduction in right atrial and peripheral venous pressures—the epidural group having the largest reductions and the inhalation anesthesia group having a greater reduction than the IPPV group. The reduction in arterial pressure is thought to result in reduced arterial bleeding. Likewise, the reduction in central venous and peripheral venous pressure lessens venous oozing at the surgical site. The differences in spontaneous and controlled ventilation are considered the result of elevated intrathoracic pressures with IPPV. In conjunction with reduced central and peripheral venous pressures during epidural anesthesia, it has also been shown that arterial and venous flow and venous capacitance are increased (23–26). It is likely, therefore, that pressure and not flow is the major determinant of blood loss.

The venous pressure, however, will be influenced by other factors besides the vasodilator effects of anesthetics and hypotensive agents. In total hip arthroplasty, for example, the lateral decubitus position places the surgical site above the level of the right atrium. The actual peripheral venous pressure at the surgical site will consequently be less than central venous pressure. This may account for the lack of correlation between central venous pressure and blood loss observed in some studies (19). It has also been suggested that regional anesthesia reduces blood loss more than general anesthesia despite similar reductions in blood pressure (27,28). This observation, however, is not a consistent finding in terms of blood transfusions (29).

Controlled Hypotension

Controlled hypotension is usually defined as reducing mean arterial pressure to 50 to 75 mm Hg. Reduced systolic blood pressure in the range of 80 to 90 mm Hg is also used (30).

History

The clinical practice of controlled hypotension in surgery was first introduced in the 1940s by Gardner, (31) in which he used the technique of hemorrhagic hypotension. Hypotension with the use of high subarachnoid block was also proposed (32). Attempts to achieve a practical approach to controlling blood loss were actively sought at this time in anesthetic and surgical history to improve operative (field) conditions. Anesthesia at the time was maintained with agents such as chloroform, ether, cyclopropane, or trichloroethylene. Hypertension with systolic blood pressures above 200 mm Hg was not uncommon (33). It was not until the 1950s, however, with the introduction of ganglionic blockers and the 1960s with direct acting vasodilators that controlled hypotension became a practical and accepted approach to reducing intraoperative blood loss (34). In current anesthesia practice, many pharmacological techniques are used to induce controlled hypotension (Table 32.1).

TABLE 32.1
PHARMACOLOGICAL TECHNIQUES IN CONTROLLED HYPOTENSION

- Neuraxial blockade
  - Subarachnoid block
  - Epidural block
- Inhalation anesthetics
  - Isoflurane
  - Halothane
  - Enflurane
- Intravenous medications
  - Beta-adrenergic blockers
  - Esmolol
  - Propranolol
  - Labetalol
- Alpha-adrenergic blocking agents
  - Phentolamine
- Calcium channel blockers
  - Nicardipine
  - Diltiazem
- Direct vasodilators
- Arterial and venous vasodilators
  - Nitroglycerine
  - Sodium nitroprusside
- Arterial vasodilators
  - Hydralazine
- Ganglionic blocking agents
  - Trimethaphan
- Purine derivatives
  - Adenosine
- Prostaglandins
  - PGE_1

Blood Conservation in Surgical Subspecialties

The best documentation that the technique of controlled hypotension reduces blood loss has come from studies in orthopedic surgery, particularly total hip replacement. Sollevi (30) in 1988 reviewed the literature for controlled prospective studies back to 1974. Thirteen studies were cited in his review. The collective findings were that patients undergoing total hip replacement, irrespective of the anesthetic technique, had a reduction in blood loss of approximately 50%. He also noted that there were no major differences in blood loss despite the variability in hypotensive levels used in the various studies. In his review, Sollevi also looked at studies involving scoliosis, orthognathic, and cancer (cystectomy) surgeries. All demonstrated significant blood loss reductions except one evaluating orthognathic procedures.

The result of hypotensive techniques to control blood loss in spinal surgery is similar to that found in total hip arthroplasty. In both prospective (35,36) and retrospective (37–39) studies between 1982 and 1992, reduction in blood loss using controlled hypotension has been demonstrated between 27% and 42%.

In pelvic surgery, the benefits of controlled hypotension in blood conservation are also apparent. In a retrospective study of patients undergoing radical cystectomy, Ahlering et al. (40) demonstrated a 53% reduction in intraoperative blood loss in patients receiving trimethaphan for controlled hypotension. In another retrospective study of patients undergoing radical hysterectomy and pelvic lymphadenectomy, the use of nitroglycerine to reduce mean arterial blood pressure to approximately 60 mm Hg resulted in a 70% reduction in blood loss compared with the control group (41). Pelvic floor repair under controlled hypotensive anesthesia with trimethaphan was shown by Donald (42) to reduce blood loss by 50%.

CLINICAL CONSIDERATIONS

Indications and Contraindications for Controlled Hypotensive Anesthesia

The use of controlled hypotension during anesthesia must be based on clinical judgment. Knowledge of the extent of the potential benefits based on the surgical procedure must be measured in relationship to the pharmacology and/or toxicity of the hypotensive medication used and to the patient's pathophysiology. Those procedures thought to benefit most with regard to blood conservation are listed in the Table 32.2. The contraindications or relative contraindications to the use of controlled hypotension

TABLE 32.2
INDICATIONS FOR CONTROLLED HYPOTENSION

- Head and neck surgery
  - Middle ear surgery
  - Orthognathic procedures
  - Oncological surgery
  - Craniofacial procedures
- Orthopedic surgery
  - Hip arthroplasty
  - Spinal fusion
- Neurosurgery
  - Aneurysm
  - Arteriovenous malformation
  - Vascular tumors
- Pelvic surgery
  - Radical prostatectomy
  - Cystectomy
  - AP resection
  - Radical hysterectomy
- Chest wall surgery
  - Radical mastectomy
- Transfusion restrictions
  - Patient refusal

TABLE 32.3
CONTRAINDICATIONS AND PRECAUSION TO CONTROLLED HYPOTENSION

- Cardiovascular disease
  - Uncontrolled hypertension
  - Coronary artery disease
- Cerebral vascular disease
- Severe pulmonary disease
- Renal disease
- Hepatic disease
- Pregnancy
- Anemia
- Hypovolemia

TABLE 32.4
MORTALITY IN CONTROLLED HYPOTENSION

Investigators	Years	Patients	Deaths (%)
Hampton and Little (40)	1950–1953	27,930	96(0.34)
Enderby (41)	1950–1960	9,107	9(0.10)
Larson (42)	1958–1964	13,264	113(0.10)
Enderby (43)	1960–1976	9,256	2(0.02)
Pasch and Huk (44)	1977–1984	1,802	1(0.06)
Enderby (45)	1950–1979	20,558	10(0.04)

(Reprinted with permission from Van Aken H, Miller ED. Deliberate hypotension. In: Miller RD, ed. *Anesthesia.* New York, Churchill Livingstone; 1994:1481–1503.)

focus on the concern for inadequate perfusion of vital organs. Table 32.3 lists those commonly accepted contraindications to controlled hypotension.

The clinical intention indication for deliberate hypotension is to control intraoperative blood loss for the purpose of both improving the surgeon's operative field and reducing the need for homologous blood transfusions with its associated risks. Other benefits of the technique have also been proposed such as decreased incidence of infection due to reduced cauterized and ligated tissue, improved skin flap viability secondary to reduced oozing, reduced anesthetic needs, and modified systemic effects of acrylic bone cement in hip arthroplasty (14).

Complications Associated with Deliberate Hypotension

Mortality

Evaluation of mortality related to controlled hypotension has been a concern since the inception of the technique. Most studies indicate that the mortality associated with controlled hypotension is infrequent (Table 32.4). With advancing safety of anesthetic technique and monitoring plus better knowledge of the physiology and pharmacology of controlled hypotensive techniques, the incidence of complications has substantially decreased. Sollevi (30) in his review of the subject found no mortality in 13 prospective randomized studies of 764 total hip arthroplasties from 1974 to 1986. Of these studies, only one noted a single complication of reduced PaO_2.

Morbidity

Central Nervous System

Morbidity associated with controlled hypotension usually focuses on the potential threat of reduced perfusion to vital organs. Of utmost concern is cerebral perfusion. Theoretically, if mean arterial pressure is maintained above central venous pressure and oncotic pressure is also maintained (calculated at approximately 30 to 40 mm Hg), then cerebral perfusion should be adequate (14) in a healthy individual. As a margin of safety, most define the lower limits of mean pressure in a healthy individual as 50 mm Hg. The rationale for using a mean arterial pressure of 50 mm Hg is that this value represents the lowest pressure at which autoregulation of cerebral blood flow occurs (this is also true for other organs). Below this level, cerebral blood flow becomes pressure-dependent. The margin of safety may be greater in healthy individuals where normal cerebral oxygen metabolism has been shown to persist with cerebral blood flow as low as 18 mL/100 g/min; this corresponds to a mean arterial perfusion pressure of 30 to 40 mm Hg (43). Other determinants of cerebral blood flow, specifically, carbon dioxide and oxygen tensions, must also be taken into account (Fig. 32.4). In normal brain at normotension, cerebral blood flow changes approximately 2 mL/100 g/mm Hg in $PaCO_2$ (44). This relationship, however, is modified by controlled hypotension. The slope of this relationship between $PaCO_2$ and cerebral blood flow is progressively reduced as blood pressure drops such that when mean arterial pressure falls below 50 mm Hg, cerebral blood flow does not change in response to changes in $PaCO_2$ (45). Additionally, the influence of the hypotensive agent chosen to induce controlled hypotension will further modify the response of the cerebral vasculature.

In patients with cerebrovascular disease or chronic hypertension, the margin of safety may require a higher lower limit of blood pressure. Pasch and Huk (46) reviewed 1,802 patients undergoing otorhinolaryngological procedures under controlled hypotension from 1977 to 1984. Four patients suffered postoperative cerebral events, with

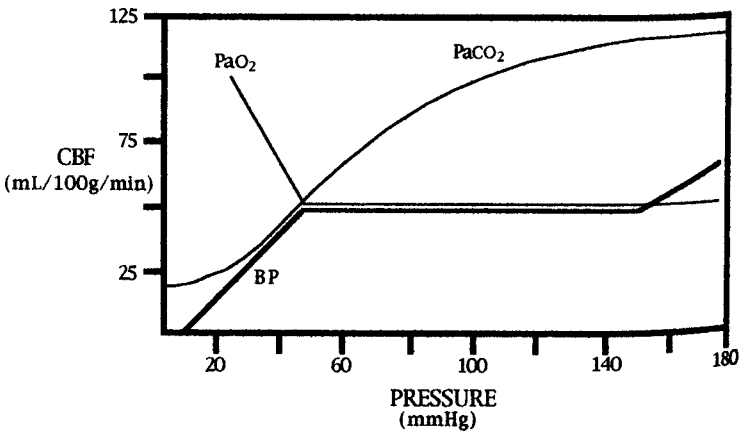


Figure 32.4 Cerebral blood flow changes due to alterations in $PaCO_2$ and blood pressure. The other two variables remain stable at normal values when the remaining value is altered. (Reprinted by permission from Shapiro HM. Physiology and pharmacologic regulation of cerebral blood flow. In: *ASA refresher courses in anesthesiology.* Baltimore, Md: J.B. Lippincott; 1977:161–178.)

one death. Two patients had preoperatively unrecognized cerebrovascular disease: one had a stenotic internal carotid artery and sustained an intraoperative stroke and one had a hypoplastic vertebral artery and died on the seventh postoperative day of generalized ischemic brain injury. The latter injury was thought to be related to positioning, although controlled hypotension may have had a contributing effect. The other cerebral injuries occurred late in the postoperative period. The morbidity related to controlled hypotension in this study was 2 of 1,802 (0.11%) and the mortality, 1 of 1,802 (10.06%).

Cerebral blood flow is also a concern in patients with hypertension. Hypertension resets the lower limits of cerebral blood flow autoregulation. Strandgaard (47) evaluated cerebral blood flow autoregulation in awake patients with untreated or ineffectively treated hypertension during controlled hypotension using trimethaphan and reverse Trendelenburg. He compared this patient population with a previously hypertensive group with well controlled hypertension on medical therapy and a normotensive group. The resting mean arterial blood pressures, the lower limit of cerebral blood flow, and the lowest tolerated blood pressures are listed for the three groups in Table 32.5. The data demonstrate that a reduction in mean arterial pressure of approximately 25% was required to reach the lower limit of cerebral blood flow autoregulation. Additionally, a reduction of approximately 55% was required to reach the mean arterial pressure at which symptoms of brain hypoperfusion occurred. The associated cerebral blood flow studies demonstrate that the autoregulation curve in the uncontrolled hypertensive patients is shifted to the right (Fig. 32.5). The autoregulation curves in the well-controlled hypertensive patients, however, were highly variable. The variability ranged from normal curves to curves shifted to the right as much as untreated hypertensive patients. It is also important to point out that in the uncontrolled hypertensive group given long-term antihypertensive therapy (8 to 12 months follow-up), cerebral blood flow autoregulation varied from normal to no evidence of change. The application of controlled hypotension, therefore, in the patient with well-treated hypertension as well as the poorly controlled hypertensive must be used with caution because the cerebral autoregulatory mechanism may not have a normal response.

In another study concerning patients with hypertension, Sharrock et al. (48) evaluated the safety of controlled hypotension using epidural anesthesia in controlled hypertensive patients undergoing total hip replacement. He found no increased incidence of cerebral hypoperfusion, myocardial infarct, or renal failure in comparing the response of induced hypotension to 52 to 55 mm Hg in nonhypertensive or controlled hypertensive groups. He also noted that no observed signs or symptoms of cerebral hypoperfusion as seen by Strandgaard (47) occurred at mean arterial pressures of 50 mm Hg as long as cardiac output was maintained (cardiac index greater than 2.0 L/min/m). The symptoms noted by Strandgaard (47) may in part be due to reduced cardiac output because the technique of reverse

TABLE 32.5
AUTOREGULATION AND CEREBRAL BLOODFLOW

	Mean Arterial Blood Pressure (mm Hg)		
Group	Rest	Limit of Autoregulation	Lowest BP Tolerated
Group 1	145 ± 17	113 ± 13	65 ± 10
Group 2	116 ± 18	96 ± 17	53 ± 18
Group 3	98 ± 10	73 ± 9	43 ± 8

Group 1, uncontrolled hypertensives; group 2, well-controlled hypertensives; group 3, normotensives. Values are given as mean ± SD.
(Reprinted with permission from Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. *Circulation.* 1976;53:723–724.)

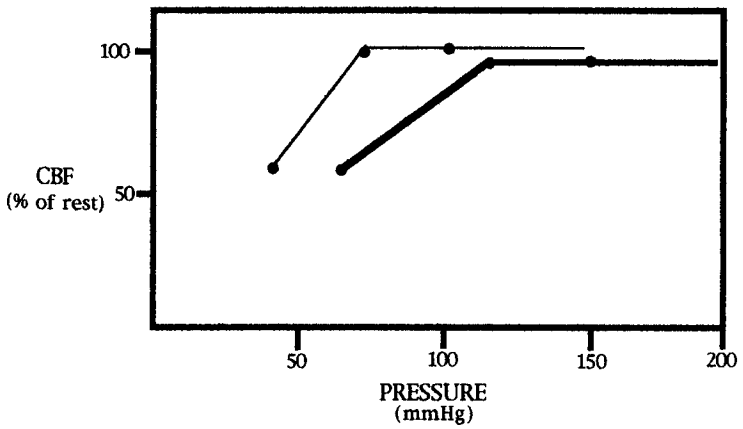


Figure 32.5 Mean curves of autoregulation of cerebral blood flow (CBF) in normotensive (light line) and severely hypertensive (heavy line) human subjects. Each curve is defined by the mean values of resting blood pressure, the lower limit of CBF autoregulation, and the lowest tolerated blood pressure. The curve from the hypertensive patients is shifted to the right on the blood pressure axis. (Reprinted by permission from Strandgaard S. Autoregulation of cerebral blood flow in hypertensive patients. *Circulation.* 1976; 53:723–724.)

Trendelenburg preload reduction plus trimethaphan afterload reduction is known to reduce cardiac output (48). In the Sharrock et al. (48) study of extradural induced hypotension to 50 mm Hg, cardiac output and stroke volume remained unchanged in both the nonhypertensive and the controlled hypertensive group. Maintenance of cardiac output is, therefore, probably of great importance for the safety of controlled hypotension in patients with a history of hypertension.

Another area of concern with regard to the central nervous system occurs during instrumentation of the spinal column. Spinal cord injury may occur during distraction of the vertebral column for fracture stabilization or spinal deformity correction, a technique frequently performed with controlled hypotensive anesthesia to reduce blood loss. It has been shown that the spinal cord is more sensitive to distraction and/or compression during controlled hypotension than at normotension as measured by reduction in somatosensory evoked potentials (36,49,50). The effect of controlled hypotension on somatosensory evoked potentials may also depend on the agent used for inducing hypotension. In the canine model, different agents have variable effects on spinal cord blood flow. For instance, sodium nitroprusside reduces spinal cord blood flow initially with associated hypotension and then blood flow returns to normal as autoregulatory mechanisms come into play. With trimethaphan-induced hypotension, no autoregulatory compensation is seen until it is discontinued. Nitroglycerine, on the other hand, has been shown to maintain control levels of blood flow throughout the hypotensive period (51). The potential for an additive effect of spinal cord distraction and controlled hypotension emphasizes the importance of intraoperative evoked potential monitoring when using controlled hypotension during these surgical procedures.

The effect of controlled hypotension on brain function as measured by neuropsychological tests has also been evaluated. In healthy individuals undergoing controlled hypotensive anesthesia, there has been no demonstration of impairment of memory or mental functions compared with patients undergoing normotensive anesthesia (52,53).

Cardiac

The primary concern with the use of controlled hypotension in relation to the heart is the supply of adequate oxygen to meet myocardial oxygen demand. Like the cerebral arterial system, progressive hypotension elicits a local autoregulatory response in the coronary arteries, resulting in vasodilatation and increased blood flow. Because the myocardium maximally extracts oxygen, an increase in myocardial oxygen requirements necessitates an increase in coronary blood flow by means of a vasodilatory response. Hypotension, therefore, reduces the coronary vasodilatory reserve.

Patients with atherosclerotic coronary artery disease have an existing impaired vasodilatory reserve due to compensatory arteriolar vasodilatation, resulting from epicardial flow impairment (54). Systemic hypotension in the presence of coronary artery stenosis will directly reduce myocardial perfusion and, depending on the extent, may result in ischemia (55). The pharmacological techniques for inducing controlled hypotension reduce ventricular work by cardiac unloading, resulting in a reduction in myocardial oxygen uptake (56). This may increase the therapeutic index of controlled hypotension in patients with coronary artery disease. However, when the pharmacological techniques used involve coronary arteriolar vasodilators such as sodium nitroprusside, adenosine, and possibly isoflurane, the potential for coronary steal exists (54,57). In contrast, medications such as nitroglycerine, which primarily cause epicardial vasodilatation as well as unloading the heart, will reduce the potential for myocardial ischemia (54). Additionally, the use of beta-1 antagonists in controlled hypotension to reduce myocardial metabolic requirements may also be beneficial in reducing the potential for ischemia (58).

Pulmonary

The effects of controlled hypotension on pulmonary function and oxygenation involve two main areas of concern: the effect on dead space and on the inhibition of hypoxic pulmonary vasoconstriction. Initial studies suggested that controlled hypotension may contribute to an increase in dead space (59). Later studies, however, found that if cardiac output is maintained, then dead space is not affected by controlled hypotension (60–62).

Vasodilators used to induce hypotension may affect oxygenation by inhibiting hypoxic pulmonary vasoconstriction. Significant reductions in $PaCO_2$ have been observed with nitroglycerine, sodium nitroprusside, trimethaphan (no longer popular and rarely used), and prostaglandin E_l (63–65). A significant deterioration in gas exchange with increased intrapulmonary shunting, however, has not been observed with isoflurane-induced hypotension (62). Sparing of significant pulmonary shunting is also observed in patients with chronic obstructive pulmonary disease (65). It is proposed that patients with chronic obstructive pulmonary disease have destructive vascular changes that increase pulmonary arterial pressures, preventing significant decreases in pulmonary vascular resistance by vasodilators. Other vasodilators also result in increased pulmonary shunting such as calcium channel blockers. Nicardipine (66) and nifedipine (67,69) have both been shown to increase intrapulmonary shunt. Little or no change has been observed with diltiazem (67). Similarly, little or no change has been observed with labetolol (67,68). Because of the potential reductions in arterial oxygenation resulting from the use of vasodilators for inducing controlled hypotension, arterial blood gas monitoring is a prerequisite for using this technique in blood conservation.

Renal

The rate of blood flow through the kidney is maintained relatively constant with arterial pressures between 80 and 180 mm Hg; a similar autoregulatory pattern holds for glomerular filtration rate (69). Below 80 mm Hg, effective renal blood flow and glomerular filtration rate fall. During controlled hypotension with mean arterial pressures reduced to 50 to 60 mm Hg urine flow rate, endogenous creatinine clearance, and osmolar clearance fall; these values return to normal with discontinuation of hypotension (70–74). Because of the return of normal renal parameters after discontinuation of hypotension, the use of controlled hypotension is not considered to be detrimental to renal function if normovolemia is maintained.

Controlled hypotension leads to the stimulation of the renin-angiotensin system in response to decreased renal perfusion. It also results in a reflex activation of the autonomic nervous system. These responses are in addition to the stress response induced by surgery itself and are variable depending on the agents used to produce hypotension. Sodium nitroprusside-induced hypotension results in the release of catecholamines and activation of the renin-angiotensin system compared with trimethaphan, which inhibits the reninangiotensin response and release of catecholamines by ganglionic blockade (75). Isoflurane, or isoflurane with labetalol, induced hypotension attenuates the stress response, reducing catecholamine release and minimizing renin activity (76,77). Adenosine triphosphate, nitroglycerine, and prostaglandin E_1 all increase plasma renin activity during hypotensive anesthesia. Norepinephrine is also significantly elevated by adenosine triphosphate, nitroglycerine, and prostaglandin E_1; however, epinephrine is elevated by nitroglycerine and prostaglandin E_l but not adenosine triphosphate (78).

Discontinuation of hypotensive anesthesia may result in a transient period of rebound hypertension due to persistence of the effects of the activated renin-angiotensin system. Sodium nitroprusside is the only drug with which this is a significant problem. The use of beta-blockade in conjunction with sodium nitroprusside, however, can attenuate this response and reduce the required dosage and reflex tachycardia associated with sodium nitroprusside (79,80). Captopril, which prevents the conversion of angiotensin I to angiotensin II, may also be beneficial in preventing rebound (81).

Hepatic

Total liver blood flow is the sum of portal venous and hepatic arterial blood flows. Total liver blood flow is held fairly constant by fluctuations in hepatic arterial flow to compensate for variations in portal vein blood flow from the splanchnic bed (82). Controlled hypotension (mean arterial pressures of 35 to 60 mm Hg) with sodium nitroprusside and trimethaphan has been shown not to change total liver blood flow (83,84). The hepatic oxygen supply, however, is largely determined by the arterial fraction from the hepatic artery (85). Concern has been raised regarding the ratio of hepatic arterial to portal venous blood flow during controlled hypotension because of the greater contribution of oxygen supplied by the hepatic arterial circulation (86). In a study by Sivarajan et al. (84) evaluation of controlled hypotension with sodium nitroprusside and trimethaphan showed no significant differences in total liver blood flow or the ratio of hepatic artery blood flow to total blood flow. In patients with normal hepatic function, therefore, controlled hypotension maintained within normal autoregulatory limits is probably not detrimental to the liver.

Eye

There have been numerous reports describing the development of unilateral or complete visual loss following cardiac and spinal surgery in the prone position, including a few recent reports by the American Society of Anesthesiologists (ASA) Anesthesia Closed Claims project (87,88). Because of the uncertain and multifactorial etiology, and rare overall occurrence of postoperative visual loss, the American Society of Anesthesiologists has established a postoperative visual loss registry in 1999. Ischemic optic neuropathy has been described following orthopedic surgery (particularly spinal surgery). Various etiologies have been proposed and may include lower mean blood pressure from deliberate hypotension and increases in intraocular pressure (from positioning) which could result in lower perfusion pressure to the optic nerve head. Hypoxia leads to destruction of axonal integrity, and free radicals that accumulate during reperfusion from ischemia may further damage the optic nerve. Patients who have a small cup-to-disc ratio (associated with compression of structures secondary to swelling) may be anatomically predisposed to developing ION. The development of this vasoconstricted shock state due to unrecognized hypovolemia is an important risk factor. When applying a deliberate hypotensive technique, the anesthesiologist must keep in mind the physiology of hemorrhage and shock, evaluate the patient for risk factor prior to surgery, be attentive to direct and indirect markers of hypoperfusion, and responsive to ischemic risk factors.

Monitoring

Arterial catheter monitoring is standard care for controlled hypotension. It not only allows for beat-to-beat measurement of the patient's blood pressure, but also allows for efficient access to obtain laboratory data (especially arterial blood gases and hematocrits) helpful in managing controlled hypotensive anesthesia. Radial artery catheters are preferred because mean arterial pressures during controlled hypotension obtained from the dorsal pedal artery are variable. With the use of sodium nitroprusside, mean arterial pressure is higher at the dorsal pedal artery than at the radial artery; with isoflurane the opposite is true (89). Direct blood pressure measurement is also preferred over oscillometry because of a tendency in the latter to overestimate blood pressure below a mean arterial pressure of 80 mm Hg (90).

Central venous pressure monitoring may also be helpful to guide fluid replacement in procedures where significant blood loss can be anticipated. Maintenance of normovolemia during controlled hypotension allows cardiac output to remain at baseline values despite a reduction in arterial pressures. The use of an urometer to track urine output is beneficial during controlled hypotension where reduced renal perfusion can be anticipated. Temperature monitoring is especially important where the vasodilator effects of hypotensive agents and epidural anesthesia contribute to reductions in body temperature. Electrocardiography and pulse oximetry should be routine. Continuous monitoring of oxygen tension with a transcutaneous sensor during hypotensive anesthesia reliably predicts changes in oxygen tension during controlled hypotensive anesthesia (91). Capnography will be helpful as a trend monitor, but it must be remembered that the end tidal and arterial CO_2 difference may be affected by controlled hypotension with its potential effect on physiological dead space and cardiac output.

Regional Anesthesia

Meta-Analysis of Blood Loss Reduction

It is a generally held observation that regional anesthetic techniques, specifically neuraxial blockade, are associated with a reduction in blood loss during surgery. This benefit has also been shown to extend to the postoperative period (92). Epidural anesthesia has been associated with lower mean arterial pressures, right atrial pressures, mean pulmonary artery pressures, and peripheral venous pressures compared with patients undergoing general anesthesia (92). Recently, several meta-analyses of the literature evaluating regional versus general anesthesia have been performed. Pitner et al. (93) evaluated 11 studies meeting the criteria of randomized controlled trials comparing regional versus general anesthesia where intraoperative blood loss was recorded. The selection of studies was compiled from review of the literature from 1966 to 1993. The pooled studies included total hip replacement ($n = 6$), hip fracture ($n = 4$), and open prostatectomy ($n = 1$). The meta-analysis revealed a significant benefit of regional anesthesia in only the total hip replacement group with a mean overall difference of 414 mL of reduced blood loss over general anesthesia (Table 32.6). Similar results were obtained in a second independent meta-analysis (94). In this analysis, the mean greater blood loss was 384 mL. Also, there was a 20% greater incidence of deep venous thrombosis and a 14% greater incidence of pulmonary embolism in the general anesthesia group compared with the regional group (both epidural and subarachnoid anesthesia). In contrast to the two meta-analyses discussed above, another meta-analysis by Sorenson et al. (95), looking at regional (epidural and subarachnoid blocks) and general anesthesia during the surgical repair of femoral neck fractures, found no difference in estimated operative blood loss. Of the 13 randomized control trials evaluated, however, only nine reported the estimated blood loss and only four gave quantitative values.

Many of these studies are limited by a lack of proper randomization, lack of suitable control groups, and low

TABLE 32.6
META-ANALYSIS OF REGIONAL VERSUS GENERAL ANESTHESIA: MEASURE OF BLOOD LOSS CHANGE

Surgery	No. Studies Positive/ Negative	Summary Effect size	Mean Overall Difference (mL)	95% Confidence Limits (mL)	Power of Negative Studies (%)
Total hip replacement	4/2	−0.89	−414	−533 to −330	24 40 6
Hip fracture	1/3	−0.08	−20	−81 to 41	5
Open prostatectomy	1/0	−1.44	N/A	N/A	N/A

(Reprinted with permission from Pitner R, Crews J, Mathieu A. Is regional anesthesia more effective than general anesthesia in reducing intraoperative blood loss [abstract]. *Anesthesiology.* 1993;79(suppl 3A):A1070.)

statistical power. In addition, arterial blood pressure, an important confounding factor was not controlled for in studies monitoring intraoperative blood loss.

Shir et al. (96) studied one hundred patients undergoing radical retropubic prostatectomy (RRP) and randomly assigned them to receive either epidural anesthesia (EA), combined epidural and general anesthesia (EG), or general anesthesia alone (GA). The mean blood loss in the EA group (1490 ± 90 mL; mean ± SEM) was significantly lower than mean blood loss in the EG group (1810 ± 100 mL) and the GA group (1940 ± 130 mL) ($p = 0.01$). The authors conclude that GA is an independent predictor of increased intraoperative blood loss. It is possible that positive pressure ventilation increases bleeding during GA. In comparison to GA, EA is more effective in reducing the need for allogeneic blood products.

Epidural Anesthesia

The benefit of regional anesthesia in reducing intraoperative blood loss was demonstrated as early as 1967. Madsen and Madsen (97) found a reduction in blood loss in patients undergoing prostatectomies with neuraxial block compared with general anesthesia. With abdominal prostatectomies, the literature indicated a reduction in blood loss in patients receiving regional as opposed to general anesthesia (98,99). In these studies, the reduction in blood loss averaged 30% to 40%. The reduction in blood loss was observed with the use of epidural anesthesia even in the presence of equivalent mean arterial blood pressures to those found in the general anesthesia group (99). More profound blood conservation has been observed when the epidural anesthesia is associated with reduced blood pressure compared with general anesthesia. In a study by Thorud et al. (98), they noted a 69% reduction in blood loss in comparing neuroleptic with epidural anesthesia where epidural anesthesia averaged lower systolic and diastolic blood pressures during the operation, although their statistical analysis failed to show a significant correlation between blood pressure and blood loss.

Pelvic Surgery

In transurethral prostatectomy (TUR-P), however, there is disagreement. Significant reductions in operative blood loss with spinal and epidural anesthesia were reported by Abrams et al. (100) in patients undergoing TUR-P. They observed a 43% reduction in blood loss in the regional group with no significant relationship between blood pressure and blood loss. Others have found no significant benefit to regional anesthetic techniques (101). Other major pelvic surgical procedures have also demonstrated. The blood-conserving effects of epidural anesthesia, including pelvic floor operations, (42,102) cystectomy, (103) hypospadias repair, (104) and cesarean section (105,106).

Boldt et al. (107) studied in a randomized prospective controlled trial that controlled hypotension was more effective in reducing allogeneic blood transfusion requirements compared to ANH. Cost-savings were demonstrated only in the group of patients who underwent intraoperative controlled hypotension.

Epidural Anesthesia Use in Major Vascular Procedures

The benefit in blood conservation with the use of epidural anesthesia, however, has not been a significant observation in major vascular procedures. In three large prospective randomized studies of general versus epidural anesthesia in patients undergoing major revascularization of the abdominal aorta and lower extremities, no significant differences were noted regarding blood loss (29,108,109). Similar observations have been described in other vascular procedures. Muskett et al. (110) studied 75 consecutive patients undergoing either deep cervical plexus blocks or general anesthesia for carotid endarterectomy. Blood loss

between the two groups was similar, and there was no significant difference in blood pressures between the two groups. The absence of benefit to blood conservation in vascular surgery may relate to the surgical technique where most blood loss is related to arteriotomy and flushing of grafts.

Controlled Hypotensive Anesthesia Combined with Epidural Anesthesia

The benefits of blood conservation in total hip replacement observed with controlled hypotension are also quite apparent with the use of epidural anesthesia (8,9,19,27,28,111). The question may then arise as to which is the better technique for blood conservation: epidural anesthesia or general anesthesia with controlled hypotension? Rosenberg et al. (28) prospectively studied 157 consecutive patients for total hip replacement. Their study evaluated four groups of anesthesia: halothane/N_2O with sodium nitroprusside controlled hypotension, halothane/N_2O without hypotension, neuroleptic anesthesia, and epidural anesthesia. The greatest reduction in blood loss occurred in the controlled hypotensive group, followed by epidural anesthesia, halothane/N_2O anesthesia, and neuroleptic anesthesia (Table 32.7). Mean intraoperative blood loss for the controlled hypotension group was 660 mL, epidural blood loss was 35% greater, halothane/N_2O blood loss was 46% greater, and neuroleptic anesthesia resulted in a 63% greater blood loss. The study sheds some insight into the importance of different anesthetic techniques with regard to surgical blood loss. In a similar study by Keith (111) without a controlled hypotensive group, a 47% increase in blood loss was seen in the halothane/N_2O group and a 54% increase in the neuroleptic group over the epidural anesthesia group.

Juelsgaard et al. (112) randomized 30 consecutive patients scheduled for total knee replacement (TKR) to hypotensive epidural anesthesia (HEA) without tourniquet or HEA with tourniquet. The authors conclude that HEA is a safe technique that allows TKR without the use of a tourniquet.

Zellin et al. (113) studied 30 consecutive patients undergoing orthognathic surgery under hypotensive anesthesia. The group that received addititional desmopressin and tranexamic acid showed significantly reduced blood loss ($p < 0.01$).

Postoperative blood loss has also been evaluated, although the results are less consistent. There is evidence to suggest, however, that if epidural analgesia is maintained postoperatively, blood loss can be reduced further (114).

In spinal surgery where controlled hypotension has proven to be an effective measure to reduce blood loss, epidural anesthesia may also play a role. In a retrospective review of 80 patients undergoing lumbar spine surgery, Greenbarg et al. (115) found a reduction in operative blood loss of 35% in patients receiving lumbar epidural anesthesia compared with general anesthesia.

Lim et al. showed that esmolol-induced controlled hypotension combined with moderate ANH was effective in reducing the number of units of blood transfused perioperatively in the esmolol-ANH group ($p < 0.01$).

Subarachnoid Anesthesia

The relationship of subarachnoid anesthesia to intraoperative blood loss is similar to that of epidural anesthesia. In a review of general versus subarachnoid anesthesia by Covino (116), 11 studies were analyzed. Of the 11 there were four studies of total hip arthroplasty performed with subarachnoid or general anesthesia. The average blood loss for the general anesthesia group was 1167 mL compared with 765 mL in the subarachnoid group. The findings in hip fracture surgery, however, are variable. In a meta-analysis by Sorenson and Pace (95) of anesthetic techniques during the surgical repair of femoral neck fractures, there were 11 of 13 randomized controlled trials

TABLE 32.7
ANESTHETIC TECHNIQUE AND SURGICAL BLOOD LOSS

Group	Intraoperative Blood loss	Postoperative Blood Loss	Total Blood Loss	Perioperative Blood Loss	Mean Arterial Pressure (mm Hg)	Operative Time (min)
Hypotensive anesthesia(I)	0.66 ± 0.07	0.60 ± 0.11	1.27 ± 0.11	1.12 ± 0.15	61 ± 1.2	105 ± 4.8
Halothane anesthesia(II)	1.22 ± 0.13	0.74 ± 0.13	1.96 ± 0.11	1.66 ± 0.23	85 ± 2.1	108 ± 5.6
Epidural anesthesia(III)	1.02 ± 0.10	0.58 ± 0.04	1.59 ± 0.10	1.62 ± 0.10	92 ± 4.5	103 ± 3.0
NLA(IV)	1.78 ± 0.35	0.84 ± 0.20	2.62 ± 0.49	2.22 ± 0.46	101 ± 3.6	109 ± 8.0

Values are mean ± SD.
(Reprinted with permission from Rosberg B, Fredin H, Gustafson C. Anesthetic techniques and surgical blood loss in total hip arthroplasty. *Acta Anaesth Scand.* 1982;26:189–193.)

performed under subarachnoid anesthesia. The other two used epidural anesthesia. The study found no difference in the estimated operative blood loss. However, as Covert and Fox (117) pointed out in their review of anesthesia for hip surgery in the elderly, the variability may be due to the operative approach and type of hip fracture. They noted that the intraoperative blood loss for internal fixation of femoral neck fractures is less than that for intertrochanteric fractures and hemiarthroplasty procedures. Further insight into this question is obtained by looking again at Sorenson and Pace's meta-analysis (95). Although the exact numbers are not discussed, they state that the vast majority of the patients had surgical repair by open reduction with internal fixation of femoral neck fractures. In two of those studies, however, where most patients had intertrochanteric fractures, intraoperative blood loss was significantly less in the subarachnoid anesthesia group (118,119).

The benefits of regional anesthesia, specifically subarachnoid block, regarding intraoperative blood conservation have also been demonstrated in transurethral prostatectomy, (97,120) lower extremity vascular surgery, (121) and colectomy (122).

Effect of Regional Anesthesia on Coagulation

Epidural anesthesia and analgesia have been associated with both direct and indirect effects on hemostasis (109, 114,123,124). Surgery performed with general anesthesia results in hypercoagulability manifested by an increase in fibrinogen and platelet activation; the opposite is true for epidural anesthesia alone or combined with general anesthesia (109,123,124). Epidural anesthesia is associated with an increase in the level of plasminogen activators and an increase in the capacity of the venous endothelium to release these activators. This effect extends to the third postoperative day (123). The benefit of such an effect is the reduction in thrombotic events in peripheral arterial grafts and the coronary arteries and the reduction in deep venous thrombosis and pulmonary embolism (29,109, 125). The potential for increased blood loss might be considered given the effects of epidural anesthesia on coagulation. In actuality, there is no difference in blood loss, (29,109) or possibly there may even be a reduction in blood loss (92).

Additionally, local anesthetics have been shown to exert an effect on hemostasis by inhibiting platelet aggregation (123). This effect occurs at clinically relevant concentrations and in a dose-dependent fashion. As pointed out by Borg and Modig, (124) local anesthetics are thought to have a stabilizing effect on all blood cells, including inhibition of leukocyte locomotion and response to endothelial injury. The effects in relation to surgical blood loss, however, are not clinically relevant.

SUMMARY

Much of the blood loss that occurs during surgery is largely dependent on the type and extent of the operative procedure. The anesthesiologist's intervention, however, can modify the degree of blood loss in many circumstances. The benefit to the surgeon is an improved surgical field, allowing greater efficiency and consequently the potential for further reduction in blood loss. The benefit to the patient resides in the reduced exposure to the need for blood transfusion with its inherent risks.

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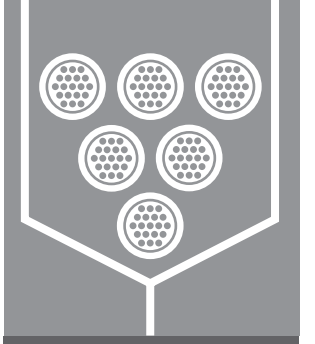

33

Perioperative Red Cell Salvage and Autotransfusion

Jonathan H. Waters

The blood management technique which offers the greatest ability to avoid red cell transfusion intraoperatively is red cell salvage. Many misconceptions and misinformation exist regarding these systems. As a result, red cell salvage is frequently viewed as ineffective and expensive. This chapter will review the multiple aspects which are important in order to apply this technology safely and effectively. The discussion will primarily focus on washed red cell salvage.

HISTORY OF AUTOTRANSFUSION

The first instance of cell salvage was carried out by Duncan in 1885 (1) when he collected a small amount of blood from an amputated limb and injected it back into the patient intravenously. In the 1920s and 1930s, a series of small case reports described blood that was collected from various abdominal cavities, strained through sterile gauze, citrated, and then reinfused to the patient. This practice resulted in adverse reactions including hemoglobinuria.

Suction apparatuses were eventually used to facilitate the collection of salvaged blood for reinfusion (2). In 1968, Wilson and Taswell (3) introduced a new apparatus that permitted blood collection, processing, washing, and reinfusion in a continuous process. With this apparatus, blood was collected from the surgical field via a suction aspirator; the blood was then fed into a continuous-flow centrifugation bowl in which the erythrocytes were selectively separated and extracted from the waste supernatant. These *washed* RBCs were then resuspended for infusion back to the patient. In 1970, Klebanoff (4) introduced a modified disposable autotransfusion apparatus that was made and marketed by Bentley Laboratories. While mechanically effective, the system resulted in many catastrophic events such as air embolization, exploding collection reservoirs, clotting blood in the collection system, and a frequent incidence of disseminated intravascular coagulation (DIC). The system was eventually withdrawn from the market.

A desire to remove the contaminants found in frozen red cells led to the development of the first practical high speed cell processor by Dr. Jack Latham at the Naval Blood Research Laboratory in the early 1970s. This system used a bell shaped centrifuge bowl now known as the Latham Bowl. This system was commercialized in the 1970s by Haemonetics Corporation for both blood banking and intraoperative autotransfusion. The operating equipment used for autotransfusion was called a *Cell Saver.* (Many health care workers refer to the *Cell Saver* not recognizing that this is a brand name.) In following years, Haemonetics was joined by Dideco, and Electromedics in providing disposables and advanced equipment. In the mid-1980s, a centrifuge bowl with straight sides and associated operating equipment was commercialized as the Baylor Rapid Autologous Transfusor, or BRAT.

INTRAOPERATIVE WASHED RED-CELL SALVAGE

Contemporary blood salvage systems rely on a combination of a reservoir for collection and a centrifugal mechanism for

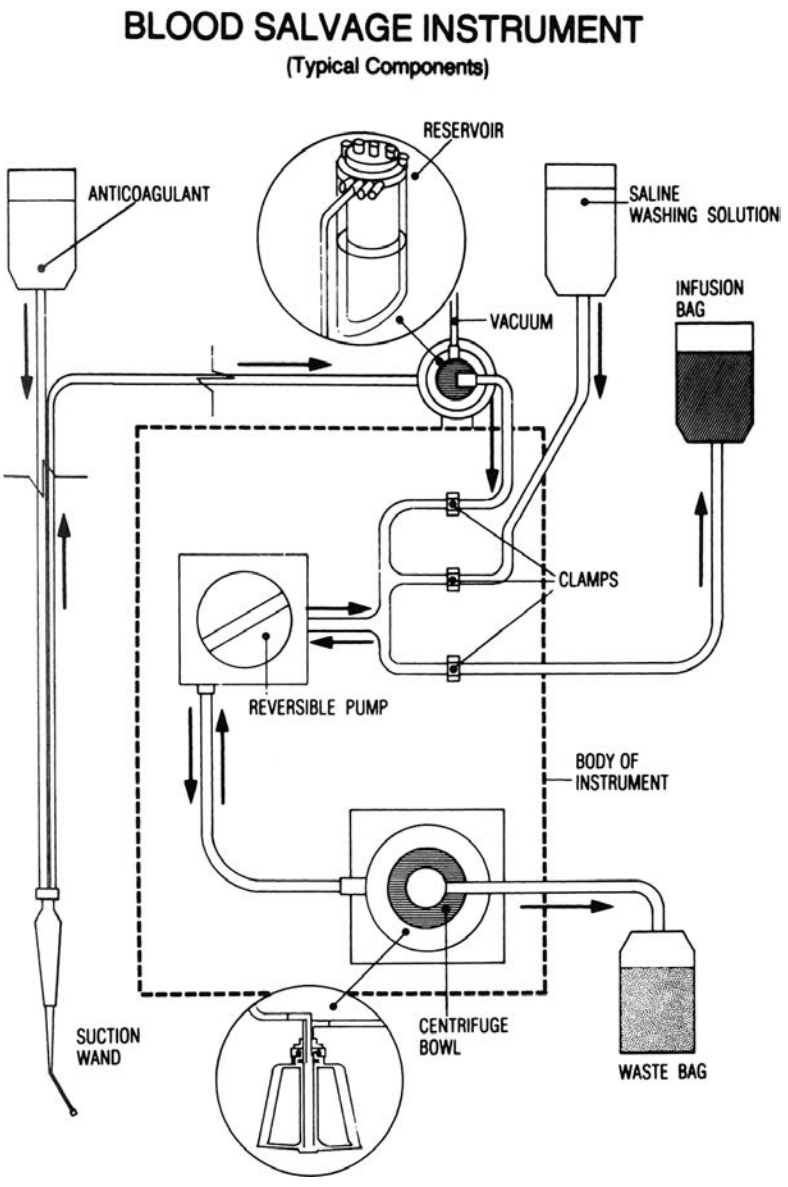

Figure 33.1 Diagram of components of a typical centrifuge-based blood salvage instrument. (Reprinted with permission from Williamson KR, Taswell HF, Rettke SR, et al. Intraoperative autologous transfusion: its role in orthotopic liver transplantation. *Mayo Clin Proc.* 1989;64:340–345.)

washing and concentrating. The typical components of a modern blood salvage device are depicted in Figure 33.1. In cases where a large volume of blood loss is anticipated, shed blood, along with an added anticoagulant solution, is aspirated into a reservoir that contains a filter to remove blood clots and tissue debris. The collected blood is pumped into a centrifuge-based cell-salvage instrument which concentrates the erythrocytes and washes them with 1 to 2 L of isotonic crystalloid solution. After such processing, the red-cell concentrate is available for reinfusion to the patient.

Cell Salvage Machine

Cell salvage machines come in several designs. They all depend on two basic principles for their function: the difference in density of blood constituents, and a balance of centrifugal and hydraulic forces in the processing bowl.

As blood is pumped from the collection reservoir, it enters the bowl through a central straw exiting from the bottom of the bowl while the centrifuge is spinning. The speed at which blood can be moved into and out of the bowl is partially dependent on the physical characteristics of this straw. For a given pressure generated by the roller pump, the resistance to flow will depend on the length of the straw and the radius of the straw. Resistance (R) to flow in a straight unbranched tube is defined by:

$$R = (8 \times \text{length} \times \text{viscosity})/(\pi \times (\text{radius})^4)$$

The radius of the straw in the BRAT bowl is greater than that of the typical Latham bowl. Because of the increased

radius, there is decreased resistance to flow which is one of the features of the BRAT bowl which allows for more rapid processing.

As the blood enters the processing bowl, the bowl is spinning rapidly to generate centrifugal force. The centrifugal force generated is proportional to the rotation rate of the rotor (in rpm) and the distance between the rotor center and the walls of the bowl. The centrifugal force is described by:

$$F = m\ (\nu^2/r)$$

Where m = mass, ν = rotation velocity, r = radius of rotation

From this equation, one recognizes that the force applied to a particle changes dependent upon its mass. Since red cells are heavier than other blood components, they will sediment against the walls of the bowl with the smaller, lighter particles (plasma) sedimenting closer to the core of the bowl.

As blood is pumped into the bowl, the hydrostatic force of the pumping will be exerted on the contents of the bowl. When this hydrostatic force is greater than the centrifugal force on the bowl contents, bowl contents will exit through the top of the bowl. As a result, the constituents of the bowl with the least centrifugal force being applied to them (plasma) will exit first. If rapid processing is required in order to keep up with massive blood loss, the filling of the bowl with blood and the subsequent washing can be speeded by increasing the pump rate. If blood or wash solution is pumped at too fast a rate, or with too great a force, the hydrostatic force will overcome the centrifugal force on the red cells, thus pushing the cells out of the top of the bowl and into the waste bag. Because of this problem, the bowl pack should be monitored in order to prevent red cells from being lost.

During bowl filling, pumping of shed blood continues until packed red cells have nearly filled the available space in the processing bowl. Filling the bowl with red cells, forces unwanted irrigation fluids and contaminated plasma into an exit port on the top of the bowl and thence to a waste bag which also holds sterile air forced from the bowl. Concentrating red cells while expressing irrigants and plasma removes 70% to 90% of the soluble contaminants in salvaged blood. However, the most damaging and hazardous contaminants are retained and concentrated in the bowl with the red cells. If reinfused, these contaminants can trigger disseminated intravascular coagulopathy. These contaminants can only be removed with certainty by cell washing. Wash solution is introduced into the red cell pack by pumping through the central straw of the processing bowl. This wash solution is generally normal saline but some have suggested that a more balanced isotonic solution such as Lactated Ringer's solution may offer slight advantages when compared to normal saline (5,6). This advantage relates to the chloride concentration of 154 mEq per L in normal saline; whereas, lactated Ringer's solution contains only 109 mEq per L (7,8).

The wash solution percolates through the red cell pack with the wash solution carrying away lighter debris and irregular agglomerates into the wash bag. Washing is considered complete when the effluent line appears clear to the eye and a wash volume of at least three times the bowl volume has been used. To empty the washed blood, the roller pump is reversed, and clean, packed red cells are pumped from the bowl through the straw and into a holding bag. Simultaneously, sterile air is drawn from the waste bag back into the bowl. Once the bowl is emptied of blood, another cycle may begin. It is important that the blood in the holding bag be moved into a transfer bag prior to readministration. Air will accumulate in the holding bag over time. If blood is administered directly from the holding bag, the patient is placed at risk of air embolism. Through the use of a transfer bag, blood is moved out of the holding bag, followed by air being burped out of the transfer bag back into the holding bag. Under no circumstances should a pressure cuff be used on the holding bag when blood is being directly reinfused into the patient.

SYSTEM OPTIMIZATION

Mathematical modeling of cell salvage has revealed that small changes in red cell processing efficiency can make large differences in the maximum allowable blood loss that a patient can tolerate prior to allogeneic transfusion therapy (9). These models suggest that a 70 kg patient with a starting hematocrit of 45% can sustain a blood loss of 9,600 mL if a transfusion trigger of 21% is used and cell salvage captures 60% of lost red blood cells (Fig. 33.2). The sustainable blood loss rises to 13,750 mL if 70% red cell recovery is achieved. This small change in red cell recovery with a large change in the ability of a patient to avoid an allogeneic blood transfusion highlights the importance of optimizing the cell salvage system.

Optimizing cell salvage can occur at multiple points in the processing. The following discussion addresses each area where optimizing red cell processing can occur.

Suction

As blood is lost, suction is applied to clear the blood from the surgical field. How this suction pressure is applied, changes the shear forces applied to the red cell. Shear forces occur anytime a fluid moves in contact with a solid surface (10). Shear-induced hemolysis can be produced with high suction pressures. So, the lowest tolerable suction pressure

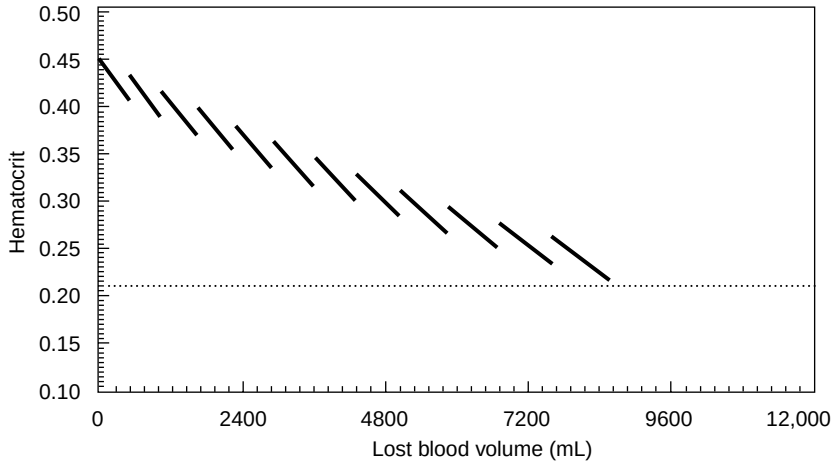

Figure 33.2 Mathematical Model of changing hematocrit during cell salvage. This figure shows the decline of the hematocrit as blood is lost during cell salvage using a mathematical model. The model is based on a 70 kg patient starting at a hematocrit of 45% with a transfusion trigger of 21%. The saw tooth pattern represents blood being lost until enough blood has been collected in order to process a unit. This unit is given to the patient that raises the patient's hematocrit. The hematocrit is never returned to its starting point because only a fraction of cells is captured and returned to the patient. In the model shown here, this efficiency of collection and return is 60%. If the efficiency changes to 70%, the model would be shifted to the right where the patient would be able to tolerate greater blood loss before crossing the transfusion trigger. If the efficiency is 50%, then the model would shift to the left where less blood loss would be tolerable. (Reprinted with permission from Waters JH, Lee JS, Karafa MT. A mathematical model of cell salvage efficiency. *Anesth Analg*. 2002;95(5):1312–1317.)

should be applied when sucking blood from the surgical field. In addition to shear-induced hemolysis, sub-hemolytic trauma can occur which will significantly shorten a red cell's life span following reinfusion.

To avoid hemolytic and sub-hemolytic stress, vacuum pressure should be regulated to 80 to 120 torr which is adequate for most surgical procedures (11,12). The vacuum level can be temporarily raised to clear the field in the event of massive blood loss then reduced to a lower level. It is important to remember that if multiple suction lines are attached to a collection reservoir, both lines need to be used simultaneously; otherwise, when one suction line is placed in blood and a separate line is sitting on top of the patient, then suction pressure will be halved.

Selection of suction tip style and the method of use can also affect the degree of shear stress and red cell recovery rates. Tips which have small caliber openings create high shear stress which can hemolyze cells during collection (Fig. 33.3). Suction tips should be immersed in the shed blood during collection. Skimming, or sucking of blood at a blood/air interface will lead to increased turbulence and shear.

Sponge Rinsing

Fully soaked gauze pads or lap sponges may contain up to 100 mL of blood (13). Of this blood, approximately 75% is retrievable by rinsing the sponge in a basin of isotonic solution (normal saline, Ringer's Lactate, Hartmann's solution) and wringing it out prior to discard. The rinse solution is then periodically sucked into the collection reservoir when the rinse solution appears to be grossly bloody.

Many fear this practice because of cotton fibers possibly being entrained into the blood from the sponge, or they fear possible bacterial contamination being introduced into the system via the sponge. In unpublished data from the Cleveland Clinic, it was found that no cotton fibers were retrievable from rinse solutions. Discussion with the manufacturer of these sponges revealed that no fiber shedding results from a tight weave of the cotton fibers and a double-washing process. In addition, macroaggregate filtering at the collection reservoir should remove large particles such as cotton fibers.

As for bacterial contamination that might result from sponge rinsing, any bacteria that would be on the sponges would have come from the surgical wound. Thus, the patient has already been exposed to the bacteria. It is well described that cell salvage blood is routinely contaminated with bacteria (14,15). This contamination has not been correlated with clinical sequelae. If sponges are suspected to be grossly contaminated with bacteria, they should simply be discarded rather than rinsed.

Anticoagulant

As blood is suctioned from the surgical field, an anticoagulant should be mixed with the blood. The purpose of the anticoagulant is to prevent clot formation in the collection

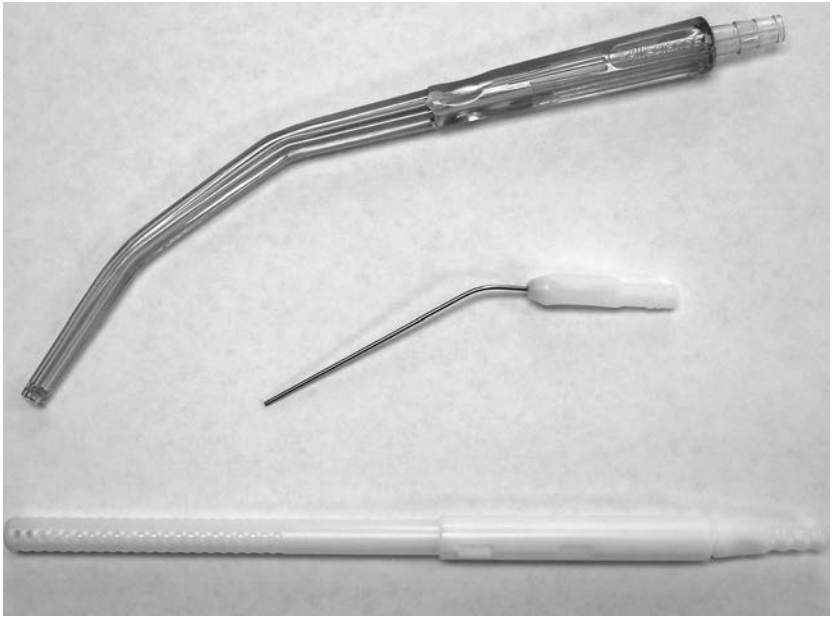

Figure 33.3 Different types of surgical suction tips. This picture shows several different types of suction tips that might be used during a surgical procedure. Each type will apply different shear forces on the red cells depending on the angle and size of the orifices.

reservoir or processing system. Clotting of blood in the collection system will result in the loss of otherwise recoverable blood as well as the need for reservoir and bowl replacement when large clots obstruct blood flow through the system. Either citrate or heparin can be used for anticoagulation during cell salvage. Some controversy exists as to which anticoagulant is best (16,17).

Due to its low cost and ready availability, heparin is most commonly used. Added to a carrier such as normal saline at a dosage of 30,000 Units per L of heparin, the solution is titrated through the aspiration suction system at a rate of 15 mL per 100 mL of collected blood. When regulating the anticoagulant rate, it is better to err on the high side rather than risk under administration and loss of red cells to clotting. Over administration of heparin during shed blood salvage is of no consequence in a cell washing system. Adequate washout will remove all but a trace of heparin with less than 10 Units residual remaining in the final blood product.

Citrate has also been used as an anticoagulant. The administration rate for citrate bearing anticoagulants (ACD, CPD, etc.) is also 15 mL per 100 mL of collected blood. Again, over use of citrate anticoagulants is better than inadequate doses. On reinfusion, rapid liver metabolism makes citrate toxicity a difficult state to achieve. In compromised liver function, correction with small doses of calcium provides immediate and nontoxic reversal. At the Mayo Clinic in Rochester, Minnesota, 15,000 units per L of heparin is mixed in a liter of the citrate solution. Use of this solution has been noted to eliminate the commonly observed cellular deposits on the interior surface of the processing bowl.

If a leukocyte depletion filter is to be used during cell salvage processing, some thought might be given to the use of heparin rather than citrate. The degree of deformability of leukocytes is reduced in the presence of calcium (18). If a leukocyte depletion filter is being used to remove bacteria, cancer cells, or amniotic fluid contaminants, this decreased deformability might also affect these contaminants. By decreasing the deformability of these cells, the ability to filter them out of the blood product may be enhanced. This is an area where further research is needed.

Collection Reservoir

The collection or cardiotomy reservoir is the collection site for blood as it awaits processing. In general, three times the size of the processing bowl is the minimum amount of blood which will be needed to fill a bowl. The reason for the three times multiplier is that the final product is concentrated into a range of 15 to 20 gm per dL hemoglobin levels. As blood is lost at hemoglobin levels much lower than this, there needs to be enough red cell mass to result in the final hemoglobin level of 15 to 20 gm per dL. In addition, some blood is destroyed during processing. Thus, approximately three times the bowl size is what is needed to process a complete bowl.

The collection reservoirs are generally available with filter sizes ranging from 40 to 120 microns. It is wise to avoid the smaller filters because residual clot and tissue debris will quickly prevent blood flow through the filter. When inadequate anticoagulation occurs and clot forms in the collection reservoir, red cells can be retrieved by mechanically agitating the reservoir while simultaneously infusing normal saline into the collection reservoir. This can be performed by

using one of the suction lines, or infusing saline directly through ports on the top of the reservoir. These ports are available on some manufacturer's reservoirs but not all. Surprisingly, large quantities of red cells can be retrieved through this mechanical agitation.

Wash Quality

In addition to optimizing red cells returned to the patient, attention to optimizing the quality of the product being readministered is required. Salvaged blood that has been poorly processed can result in adverse patient outcome. Inadequate washing has been described by Bull and Bull (19) and has been labeled, *the cell salvage syndrome.* Inadequate washing and concentration of the cell salvaged blood can lead to complications such as disseminated intravascular coagulation, or acute renal failure. This syndrome usually results when cell salvage equipment operators have received inadequate training or are simply inattentive to appropriate processing.

In order to optimize the blood quality being returned to patients, the American Association of Blood Banks (AABB) has issued perioperative standards (20) to guide in the manufacture of a cell salvage product. In addition, a guidance document (21) is available which instructs the reader in how to comply with these standards. Implementation of these standards is mandatory if cell salvage is to be performed safely. Primary to these guidelines is the requirement for dedicated personnel to operate the equipment.

In many institutions this guideline is not followed. Under this circumstance, cell salvage is frequently instituted by the operating room circulating nurse who has other operating room responsibilities, and frequently, little training in safe cell salvage application. As the surgical procedure proceeds, large quantities of blood will collect in the cell salvage collection reservoir at the same times as when the circulating nurse's responsibilities are greatest. As a result, nurses will process the blood at their convenience. Periodically pressing the start button on the cell salvage machine as he or she passes by conducting other tasks in the operating room. Thus, no observation takes place of the adequacy of processing.

This processing by convenience is highlighted by an article on cell salvage from the Cleveland Clinic, in an era prior to dedicated cell salvage personnel. O'Hara et al. (22) reported on a lack of red cell avoidance with cell salvage in patients undergoing abdominal aortic aneurysm repair. They reported an average cell salvage unit hematocrit of 31%. Hematocrits of cell salvage blood should range between 40% and 75% depending on the method of processing. Lower hematocrits in the salvaged unit will hemodilute patients negating any positive benefit. Additionally, this lower hematocrit suggests that inadequate red cell concentration has taken place thus leaving residual cellular contaminants in the blood. In this circumstance, the circulating nurse was not observing the equipment and frequent partial bowls were being washed. This early wash was being triggered by excessive hemolysis in the salvaged blood due to inattentiveness to minimizing shear forces on the red cells.

In addition to mandating dedicated personnel for this equipment, the AABB standards require a measure of the quality and concentration of the product produced. Quality indicators are of a controversial nature. Some practitioners advocate periodic albumin washout while others advocate potassium washout (21). Free hemoglobin has also been advocated. At the Cleveland Clinic Foundation, evaluation of the color of the effluent wash solution is used as a measure of the washout quality. This practice stems from a close correlation between the elimination of free hemoglobin and the color of the effluent solution. Many practitioners also periodically measure bacterial contamination. As has been previously discussed, bacterial contamination of salvaged blood is routine and little correlation is found with clinical sequelae.

In addition to a measure of wash quality, a measure of concentration is also recommended. Hematocrit or hemoglobin concentration is simply measured and can be performed on all units of blood. Adequate concentration is important to assure washout of cellular contaminants. Several of the manufacturers of cell salvage equipment are now incorporating devices within their system to measure hematocrit.

Partially Filled Bowls

The red cell content of salvaged blood is seldom known, so it is quite common to process what seems like an adequate amount of collected blood only to find that not enough cells are present to fill the bowl. This is termed a *partial bowl*. Washed, partial bowls will have biochemical contaminants removed to a greater extent than a full bowl but the concentration of cellular contaminants will be greater than a bowl which has been washed when completely filled (23,24). This higher concentration of cellular contaminants may place the recipient at risk of possible coagulation dysfunction.

Many practitioners recommend discarding partial bowls rather than risk coagulopathy. Several options exist for handling a partial bowl rather than discarding it. The first option is to ignore the risk and readminister this partial bowl. Generally, the amount of red cell mass present in a partial bowl does not warrant taking this risk. A second option is to move washed packed cells from the holding bag back into the processing bowl using the *concentrate*

function key. Reprocessing of washed cells does them no harm, and ensures adequate washing of the residual blood while increasing overall recovery rate. A third option is to return the blood to the collection reservoir, and then refill the bowl at a higher fill speed. Using the higher fill speed decreases the packing of the red cells so that fewer cells are needed to fill the bowl. Generally, this option only works when a full bowl is nearly achieved at regular fill rates. A fourth option would be to filter the partial bowl with a leukocyte depletion filter. This filter will remove most cellular and particulate contaminants thus making it acceptable for readministration.

CLINICAL INDICATIONS FOR CELL SALVAGE

The American Association of Blood Banks currently recommends the following general indications for cell salvage use: the anticipated blood loss is 20% or more of the patient's estimated blood volume; blood would ordinarily be cross-matched; more than 10% of patients undergoing the procedure require transfusion; the mean transfusion for the procedure exceeds one unit (25). These recommendations are derived from the comparison of allogeneic blood costs to perceived cell salvage cost. Since these recommendations were developed, the cost of allogeneic blood has escalated while a better understanding has been gained of the costs associated with cell salvage. For these reasons, implementation of cell salvage should be considered when much smaller amounts of blood loss are anticipated.

Accurately predicting the probability of sizeable blood loss and need for allogeneic transfusion is difficult. Because of a lack of predictability, implementation of cell salvage should start with a collection system which would entail a cardiotomy reservoir, a suction line, and an anticoagulant. This collection or standby setup costs comparably to the reagent costs for typing and crossing two units. Though a major paradigm shift, hospitals should consider implementation of a standby setup rather than the type and cross. In cases where the blood loss is certain such as in a thoraco-abdominal aneurysm repair, it is reasonable to bypass the standby setup and set up all components necessary to process blood.

There are many types of cases where cell salvage might be indicated. The types of cases should be individualized by the institution and the surgeon performing the procedure. The patients starting hematocrit, gender, age, and body weight can all influence the risk of receiving blood products (26). Table 33.1 lists many of the surgical procedures which should be considered for blood salvage.

Lastly, Jehovah's Witnesses, who refuse allogeneic blood on religious grounds, should be considered for cell salvage even if the risk is minimal to moderate of having significant blood loss. Like dialysis or the cardiopulmonary bypass circuit, many Jehovah's Witnesses feel that blood that maintains some form of continuity with their vascular system is acceptable and compatible with their beliefs. The

TABLE 33.1
GENERAL INDICATIONS FOR CELL SALVAGE

Specialty	Surgical Procedure	Comments
Cardiac	Valve replacement	
	Redo bypass grafting	
Orthopedics	Major spine	
	Bilateral knee replacement	
	Revision hip replacement	
Urology	Radical retropubic prostatectomy	Individualized by surgeon
	Cystectomy	limited to patients with prior radiation therapy
	Nephrectomy	When tumor involves major vessels
Neurosurgery	Giant basilar aneurysm	
Vascular	Thoracoabdominal aortic aneurysm repair	
	Abdominal aortic aneurysm repair	Should be individualized by surgeon and patient characteristics
Liver Transplant		
Other	Jehovah's Witnesses	When accepted by patient
	Unexpected Blood loss	
	Red cell antibodies	

TABLE 33.2
CONTRAINDICATIONS TO CELL SALVAGE

Pharmacologic Agents
Clotting agents (Avitene, Surgicel, Gelfoam, etc.)
Irrigating solutions (Betadine, Antibiotics meant for topical use)
Methylmethacrylate
Contaminants
Urine
Bone chips
Fat
Bowel contents
Infection
Amniotic Fluid
Malignancy
Hematologic Disorders
Sickle Cell Disease
Thalassemia
Miscellaneous
Carbon Monoxide (Electrocautery smoke)
Catecholamines (Pheochromocytoma)

continuous circuit is created by spiking the holding bag with an intravenous infusion line and then connecting the line directly into the patient's intravenous line. This is followed by priming of the system with normal saline so that a fluid path is always maintained.

Contraindications

The list of contraindications to cell salvage is extensive; however, most contraindications are relative rather than absolute (Table 33.2). Many of the perceived risks associated with cell salvage are theoretical risks with little clinical evidence supporting the contraindication. When a decision is being made to not use cell salvage, it needs to be considered in light of the known risks associated with the alternative therapy which is allogeneic blood.

Relative contraindications to cell salvage encompass a wide range of materials that, if incorporated into the salvaged blood product, could potentially injure the patient upon readministration. Definite contraindications would include anything that results in red cell lysis. This would include sterile water, hydrogen peroxide, and alcohol. If blood is washed, with these solutions or a hypotonic solution is aspirated into a collection reservoir, these solutions will result in red cell hemolysis. If the blood is administered it could result in renal insufficiency and failure, decreases in hematocrit, elevations in serum lactate dehydrogenase, increases in total serum bilirubin concentration, disseminated intravascular coagulation, and, potentially, death (27,28).

Many contraindications to cell salvage are not as definitive. This would include blood aspirated from contaminated or septic wounds, obstetrics, and malignancy. The use of cell salvage in these circumstances is variable from practice to practice, and advocated as safe and effective by some investigators. In certain circumstances or under life-threatening conditions the physician in charge may make the medical decision to proceed with autotransfusion. For this reason, discussion of each of these clinical areas will follow.

If cell salvage is applied in one of the contraindicated areas, additional safety in the application of cell salvage might be achieved through the use of a double suction setup. In this setup, one suction line should be connected to the cell salvage reservoir and used for suctioning of blood, while the other should be connected to the regular wall suction and used for aspiration of contaminant (29–31) By using separate suction devices, the contamination of the salvaged blood could be further minimized. The smaller the overall contamination of the salvaged red blood cells, the lower the resultant concentration in the washed product. Though this recommendation seems logical and intuitive, it is yet unproven.

Bacterial Contamination

Bowel surgery, penetrating trauma to the abdomen, or surgery where an infected wound is involved present a circumstance where shed blood might be contaminated with bacteria. In this scenario, the fear is that readministration of this blood might lead to bacteremia or sepsis.

The issue of bacterial contamination of blood has been of intense interest to the blood banking community due to 500 to 750 severe reactions or death that occur each year from bacterial contamination of blood products (32). In a surveillance study by Yomtovian et al., (33) eight bacterially contaminated pools of platelets were administered to patients, five had no symptoms with bacterial loads ranging from the 10^2 to 10^{11} cfu per mL while the others had symptoms with bacterial loads ranging from 10^6 to 10^8 cfu per mL. This study plus that of others would suggest that the type of bacteria is more important than the quantity (34–36).

The impact of cell salvage processing on blood that has been bacterially contaminated was first investigated by Boudreaux (37) who inoculated expired units of blood with bacteria and found that washing was capable of reducing contamination to 5% to 23% of the starting contamination. In a similar study, Waters et al. (38) found an approximately 99% reduction in bacterial contamination when the combination of cell washing and a leukocyte depletion filtration was performed. In the same paper, a dose response curve was generated which showed that 99% reduction of a starting load of bacteria of 10^7 still left 10^5

bacteria. This level of contamination was identified to occur in surgical procedures where gross fecal contamination of the blood was observed.

Surprisingly, bacterial contamination of cell salvage blood appears to be routine. Bland found that bacterial contamination of cell salvage blood in cardiac surgery approaches 30% of the units processed and readministered (15). Kang et al. (14) reported that 9% of the blood returned to liver transplant patients had bacterial contaminants usually of skin origin. Contamination from skin flora has been assumed to be inconsequential but the contaminants of frank stool have been thought to be different. This area has also been investigated primarily in trauma where several authors have reported on frank stool contamination of reinfused, salvaged blood yet, no increased sepsis rates were noted (39–41). In most surgical procedures, broad-spectrum antibiotics are routinely used. Several studies have suggested that these drugs add additional safety when contaminated blood is readministered (42,43).

In summary, the points to keep in mind include a recognition that during the course of most operations, a bacteremia is present. Secondly, allogeneic blood obtained from the blood bank is not bacteria-free (44–47). Lastly, postoperative infection rates are lower in patients receiving autologous blood when compared to homologous blood because of immunomodulation which occurs following homologous blood exposure (48). Dzik and Sherburne (49) in a review of the controversies surrounding cell salvage pointed out that allogeneic transfusion leads to an increase in infection rate and that when faced with bacterial contamination of cell salvaged blood, a clinical decision needs to be made as to which therapy offers the least risk to the patient.

Obstetrics

The primary concern with applying cell salvage in obstetrics is the entrainment of amniotic fluid into salvaged blood. Theoretically, this entrained amniotic fluid may cause an amniotic fluid embolism upon readministration. The mechanism for amniotic fluid embolism is not clear; therefore, any studies demonstrating that salvaged blood is clean for one parameter may not extrapolate to the unknown mechanism of amniotic fluid embolism. Bernstein et al. (50) demonstrated that amniotic derived tissue factor, a component of amniotic fluid thought to be associated with disseminated intravascular coagulopathy, is completely eliminated with washing. Again, tissue factor may be one of many elements that lead to the amniotic fluid embolism (51,52); thus, washing of this tissue factor would not assure that amniotic fluid embolism would not occur. Some investigators (53,54) feel that particulate contaminants may be responsible for amniotic fluid embolization. Durand (55) showed that, despite washing, cell salvaged blood still contained significant fetal squamous cells, fetal hemoglobin, and bacterial contamination. We have found that leukocyte depletion filters are highly effective at removing these particulate contaminants (56). The filters work through the use of a small-pore microfiber web and a negative surface charge (57).

Despite these concerns about adequate washing and amniotic fluid embolism, investigators have proceeded to administer cell salvaged blood in obstetrics. Three reports encompassing approximately three hundred patients (31,58–59) have now been published where cell salvaged blood was readministered to a bleeding parturient. This readministration was without filtering. No evidence of amniotic fluid embolism were reported in these patients suggesting that it is indeed safe. No impact on the coagulation system from readministering cell salvage blood has also been noted (60).

Despite these reports, several precautions should be taken when salvaging blood in obstetrics. First, minimizing the aspiration of amniotic fluid through a double suction setup is advisable. One suction should be connected to the cell salvage reservoir and used for suctioning of blood. The other should be connected to the regular wall suction and used only for aspiration of amniotic fluid. In this way, the volume of amniotic fluid contamination is minimized. Secondly, the utilization of leukocyte reduction filters at the completion of processing can reduce the fetal squamous cell contamination to a level comparable to maternal blood contamination. Lastly, fetal red cell contamination is present. An Rh incompatibility between mother and infant may suggest that the Rhogam dose following delivery may need to be modified. This issue is yet to be studied.

The leading cause of death during childbirth is hemorrhage so the use of cell salvage would naturally be attractive. In this circumstance, shed blood can be contaminated with bacteria, amniotic fluid, and fetal blood. Amniotic fluid contamination is feared because of the potential to create an iatrogenic amniotic fluid embolus. Support for the use of cell salvage in obstetric hemorrhage now encompasses 390 reported cases where blood contaminated with amniotic fluid has been washed and readministered without filtration (20,21,61–63). Unfortunately, the incidence of amniotic fluid embolism ranges from 1:8,000 to 1:30,000 deliveries. The rarity of this syndrome makes study of the safety of cell salvage impossible. Additionally, the mechanism or cause of the syndrome is unknown. Thus, we are left to look at markers which we think might be associated with the syndrome.

Tissue factor is thought to be involved in the disseminated intravascular coagulopathy that typically follows the

acute embolic event (64). Bernstein et al. (50) evaluated the washout of tissue factor and found that routine washing eliminated all tissue factor activity. Unfortunately, tissue factor may be only one of many components that lead to the syndrome of amniotic fluid embolism thus, washing of this tissue factor would not guarantee that amniotic fluid embolism would not occur (65,66). Several studies (67,68) assessing the removal of free hemoglobin, bromocreosol green dye, and heparin from salvaged blood would suggest that if one factor is effectively removed than the other factors are equally removed. Therefore, if tissue factor is effectively removed from blood contaminated with amniotic fluid, these previous studies would suggest that the other components of amniotic fluid would also be similarly removed or reduced significantly in concentration.

Some investigators (54,69) feel that particulate contaminants are responsible for amniotic fluid embolization. Durand et al. (55) showed cell washing did not remove fetal squamous cells. Waters et al. (56) demonstrated that leukocyte depletion filters along with cell washing will remove fetal squamous cells to an extent comparable to the concentration of these cells in a maternal blood sample following placental separation. From this study it was concluded that the combination of cell salvage washing and filtration produces a blood product comparable to maternal blood with the exception of the fetal hemoglobin contamination.

The significance of fetal red cell contamination is unstudied. Fetal blood is routinely entrained into the maternal circulation upon delivery; therefore, our supposition is that the fetal red cell contamination is insignificant except when there is a red cell antigen incompatibility between mother and infant. Isoimmunization can occur from this exposure leading to erythroblastosis in subsequent pregnancies. ABO incompatibility tends to be a minor problem when compared to Rh incompatibility. To prevent isoimmunization, anti-D immune globulin (Rhogam) is administered to the mother neutralizing this immune response. The immune globulin is administered based on a calculation of the volume of fetal red cells transferred to the mother (Kleihauer-Betke test) (70). If cell salvage blood was administered under the circumstances of an Rh incompatibility, it would seem logical to measure the maternal fetal hemoglobin concentration after cell salvage blood has been administered so that the immune globulin dose is adequate to neutralize these additional cells.

Malignancy

The last area of controversy is cell salvage in cancer surgery. As mentioned earlier, immunomodulation occurs with allogeneic transfusion. The issue of whether this immunomodulation affects tumor growth is unresolved; however, there is substantial retrospective evidence to suggest that outcome is worse for patients undergoing cancer surgery when they received allogeneic blood (71–73). Thus, avoidance of allogeneic blood is important. Likewise, administration of tumor laden blood from cell salvage would also seem to be contradictory to a good patient outcome; however, during tumor surgery, hematogenous dissemination of cancer cells is common and does not correlate with outcome (74–76). For cell salvage during tumor surgery, the use of leukocyte depletion filters is advocated. These filters have been used for filtration of malignancy in cell salvage for urologic surgery, (77,78) pulmonary surgery, (79) and in a variety of cell lines which were used to contaminate discarded blood (80,81). These studies all concluded that leukocyte depletion filters were highly effective at removing tumor cell contamination. One investigator feels that irradiation of salvaged blood contaminated with tumor is the method of guaranteeing no viable tumor cells (82,83). Though this method seems reasonable, irradiation of a cell salvage product is impractical in most hospitals. Two recent outcome studies (84,85) of patients undergoing radical prostatectomy have compared cell salvage blood to autologous blood or no blood transfusion. These studies found no difference in cancer recurrence suggesting that cell salvage is equivalent to autologous transfusion and may even be better than allogeneic transfusion for patient survival.

Microfibrillar Collagen

Microfibrillar collagen can be applied to a surgical wound in multiple different forms including sponges and powder. Microfibrillar collagen is not removed from the salvaged blood during the washing procedure, and infusion of units containing this material has caused significant morbidity and mortality in animals (86). Microfibrillar collagen is also not completely removed by passage through the typical 20-μm filter, (87,88) but recent evidence suggests that leukocyte-depletion filters do eliminate this compound (86).

COMPLICATIONS OF BLOOD SALVAGE

The process of blood salvage is associated with few complications. Air embolism is a concern if the reinfusion bag of the cell-salvage circuit is directly connected to the patient's vascular access (89). This complication can be prevented by simply transferring the blood into a separate blood bag before administration with the blood bag being burped of its air prior to sealing. When using a leukocyte depletion filter (Fig. 33.4), the filter should be given to the anesthesiologist for use. These filters should be changed after every

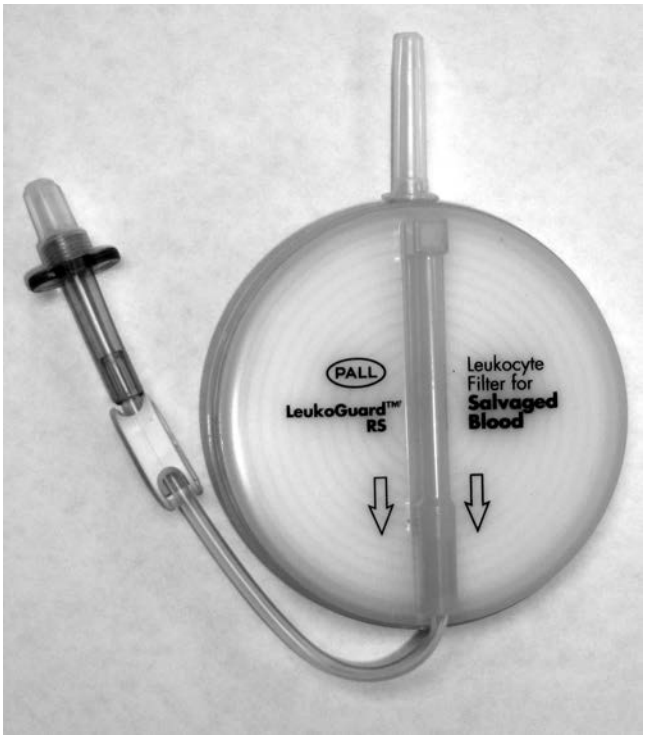

Figure 33.4 Leukocyte depletion filter. This filter will slow the readministration of cell salvage blood however it removes high percentages of many different types of contaminants.

500 mL of blood. A blood pressure bag pressurized to 300 mm Hg should be applied to the cell salvage unit in order to move the red cells through the leukocyte depletion filter. Pressures greater than 300 mm Hg will pressurize contaminants through the filter. If the autotransfusionist places the filter between the holding bag and the transfer bag, air in the unit will not be able to be removed.

Blood salvaged during removal of pheochromocytomas has been shown to cause hypertension in patients after reinfusion, (90) because extensive washing does not completely eliminate epinephrine and norepinephrine. Likewise, oxymetazoline (Afrin®) nasal spray, which is sometimes used during ENT surgery, may remain in salvaged blood in high enough concentrations following washing that hypertension and tachycardia may ensue following readministration.

Operative Blood Loss Calculations

During cell salvage, estimation of blood loss is difficult because the blood in the wall suction canisters is not available to estimate blood loss. For this reason, an estimate of blood loss can be achieved through the use of the following equation (91).

$$\text{Blood Loss} = \frac{(\text{Hs}/\text{Hp}) \times \text{Vb} \times \text{Nb}}{\text{SE}}$$

Where:

Hs = Average Hct of washed salvaged red cells
Hp = Average patient Hct during salvage
Vb = Volume of the processing bowl
Nb = Number of bowls processed
SE = Estimated salvage efficiency

Salvage efficiencies can vary depending on vacuum levels, sucker tip size, diligence of salvaging efforts, contact time of blood in the wound, and other factors. With good procedural methodology, 60% of lost red cells can be recovered (SE). As the quality of the salvage effort declines, so does efficiency of recovery, and assignment of lower values may be appropriate.

EXAMPLE 1: During abdominal aortic aneurysm repair, four bowls of 225 mL each were salvaged and returned. Low suction levels were used, lap pads (swabs) were washed, and the surgeons applied anticoagulation to the wound site to prevent clotting. Salvage efficiency was felt to be optimal at about 60%. Measured hematocrit in the washed cells was 61%, 63%, 66%, and 63% with an average of 63%. Patient hematocrits measured during the respective collection periods were 37%, 33%, 32%, and 30%, averaging 33%. Using these numbers, blood loss is calculated as follows:

$$\text{Blood loss} = (63\%) \times (225\text{mL/bowl}) \times (4 \text{ bowls})/(33\%) \times (60\%) = 2{,}863 \text{ mL}$$

UNWASHED BLOOD SALVAGE

Readministration of shed blood that has not been washed is controversial. This blood usually takes the form of blood from wound drains or chest tube drainage. The controversial decision to wash or not wash salvaged blood is often made at the institutional level but may be made by the anesthesiologist, surgeon, or both physicians together. Issues to be considered include the type of surgical procedure, the estimated blood loss and salvaged-blood volume, the composition of the shed blood, and the rapidity of bleeding. Proponents of washing believe that it removes potentially harmful substances and that the simultaneous concentration of salvaged red cells is advantageous. Others claim that such processing is unnecessary, adding only time and expense to the procedure.

Unprocessed blood has been shown to contain elevated levels of C3a, C5a, and terminal complement complexes (92); an altered lipid profile (93,94); measurable amounts of methylmethacrylate (orthopedic bone cement); and fat particles (95). The presence of these materials raises concern regarding the safety of infusing unwashed salvaged blood. Faris et al. (96) reported a 22% incidence of febrile reactions

accompanying the transfusion of unwashed autologous blood that was collected from joint drainage 6 to 12 hours after operations. However, unprocessed shed blood has been administered to many groups of patients in numerous studies with minimal ill effects. Much of this success may be related to the limited amount of unprocessed blood that is infused (usually less than 1 L) and to the limited collection periods (usually less than 6 hours). This risk of complications must be addressed in the context of the amount of mediastinal or drained blood that is directly transfused. Caution should be exerted if over 1 L of blood is being retransfused or if the patient appears to be bleeding more; with less than 1 L, reinfusion of unwashed blood is likely safe.

Because thrombosis and fibrinolysis are activated during and after operations, shed blood contains decreased amounts of coagulation factors and increased levels of FDPs (97). Fibrinogen levels are typically low in mediastinal and joint drainage; such blood does not usually clot and anticoagulation may not be needed during collection. Concern about the reinfusion of unwashed salvaged blood has focused on FDP potential to initiate coagulopathy.de Haan et al. (98) have also suggested that fibrin monomers and tissue-type plasminogen activator-stimulating activity in shed mediastinal blood potentiate the platelet dysfunction seen after CPB and lead to increased postoperative bleeding.

Schaff et al. (99) studied patients receiving shed mediastinal blood and control subjects and found no difference between the groups in the prothrombin time, activated partial thromboplastin time, fibrinogen, and FDPs. Others have found increases in fibrinolytic products in the reinfused blood, but the effect on patients was transient. Griffith et al. (100) found extremely high titers of FDPs in mediastinal blood. They compared the level of FDP in mediastinal blood that was both washed and unwashed. FDP titers were significantly elevated in the unwashed mediastinal blood, but no differences were found in the bleeding or coagulation parameters of the patients.

Postoperative salvage may not reduce the need for allogeneic transfusions (101–104). The assessment of such efficacy has been problematic because of numerous other changes in transfusion practices over the last decade. These changes include improved surgical technique, the use of pharmacological agents to decrease blood loss, increased availability of preoperatively donated autologous blood, altered criteria for allogeneic transfusion, and the use of ANH. Controlled, randomized, and blinded trials are also difficult to perform. Thus, conclusions regarding effectiveness in today's clinical setting may be different from those found in earlier investigations. Determinations of efficacy may also need to be done, at least to some degree, at the local level.

SUMMARY AND CONCLUSION

Many factors influence the efficacy of cell salvage processing. The ability of this technology to avoid allogeneic transfusion is directly dependent on the skill of the operator and the processes that are established to ensure that a high quality blood product is produced. If the guidelines outlined in this article are followed, most red blood cell transfusions become unnecessary.

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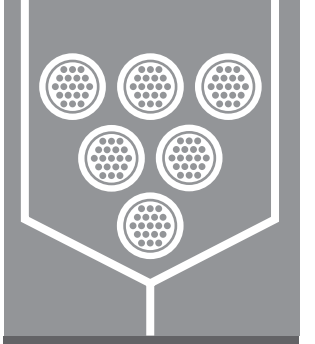

34

Intraoperative Acute Nomovolemic Hemodilution

Aryeh Shander *Tanuja Rijhwani*

Heightened awareness in the medical community and among the public over the risks associated with the transfusion of allogeneic blood products has generated renewed interest in strategies to reduce allogeneic blood product transfusion. Ferguson et al. (1) performed a series of cross-sectional survey assessments and studied the perceptions of risk associated with blood transfusion among 88 general practioners, 141 anesthesiologists, 20 journalists, and 250 blood donors. They also studied whether or not participants, given the choice, would choose to have a transfusion of donated blood or a blood substitute. The risks of transfusion of blood products have been recognized for many years; in the past few decades, increased concerns about the transmission of viral pathogens in banked blood have motivated a reevaluation of transfusion practices and a search for better blood management in an effort to reduce recipient exposure to allogeneic transfusions. In an editorial, Dodd (2) estimated the current risk of serious or fatal transfusion-transmitted disease to be about 3 in 10,000 blood recipients. Transfusion-associated morbidity includes hemolysis, post-transfusion hepatitis, transfusion-related acute lung injury, anaphylaxis, and acquired immunodeficiency syndrome (Table 34.1). A detailed discussion of infectious risks and transfusion safety is beyond the scope of this chapter. Although safety of banked blood continues to improve, we must continue to develop strategies and techniques to further reduce the exposure and complications associated with allogeneic blood transfusion.

Another reason to reduce allogeneic transfusions is that a greater number of hospitals are transfusing more blood, thereby rapidly depleting the already stretched blood supply in this country. This factor necessitates the judicious use banked blood reserves. Furthermore, it is estimated that over two thirds of all RBC transfusions in the United States are given in the perioperative period, emphasizing the sizable impact that perioperative transfusion practices (primarily guided by anesthesiologists and surgeons) can have on the demand for banked blood (3).

One method to reduce perioperative allogeneic blood transfusion is by availing autologous blood. Transfusion of autologous blood eliminates the risk of transfusion-transmitted viral disease and isoimmunization (alloimunization) directed at foreign RBC, platelet, and leukocyte antigens (4). The use of autologous blood is also desirable for patients with multiple RBC antibodies or a rare blood phenotype. Autologous blood can be collected preoperatively as whole blood or blood components; intraoperatively as fresh whole blood, acute normovolemic hemodilution (ANH), salvaged RBCs, or platelet rich plasma (PRP); and postoperatively from chest-tube or wound drains. Advances in the development of autotransfusion equipment have greatly contributed to the expanded clinical application of blood salvage procedures.

Physicians must use multidisciplinary resources to evaluate the exposure risks, benefits, and expenses of autologous and allogeneic transfusion for the best patient outcomes. This chapter focuses on the options available to physicians to reduce the amount of transfused allogeneic blood products. We focus on an intraoperative technique, Acute Normovolemic Hemodilution (ANH) that conserves autologous blood or blood components and alert the reader that ANH is one of multiple procedures and approaches that

TABLE 34.1
ADVERSE EFFECTS ASSOCIATED WITH TRANSFUSION OF BLOOD AND BLOOD COMPONENTS

	Approximate Frequency		
	Ratio	%	Reference
Effect/risk factors			
Immediate			
Acute hemolytic transfusion reaction	1/250,000–1/1,000,000	0.0004–0.0001	2
Febrile, nonhemolytic transfusion reaction	1/200	0.5000	3
Allergic reactions	1/100–1/300	0.2000	3
Hypervolemia	Variable		3
Noncardiogenic pulmonary edema	1/5,000	0.0200	3
Bacterial contamination:			
RBCs	1/500,000	0.0002	2
Platelets	1/12,000	0.0083	2
Anaphylactic hypotensive reactions	1/150,000	0.0007	3
Complications of massive transfusions (hemostatic defect, hypothermia and metabolic abnormalities)	Unknown		3
Transfusion-related acute lung injury	1/5,000	0.0200	2
Delayed			
Delayed hemolytic transfusion reaction	1/1,000	0.1000	2
Red blood cell alloimmunization	1/100	01.000	3
Leukocyte/platelet alloimmunization	1/10	10.000	3
Hemosiderosis	Unknown		3
Graft-versus-host disease	Rare		3
Posttransfusion purpura	Rare		3
Viral infection			
Hepatitis A	1/1,000,000	0.0001	1
Hepatitis B	1/220,000	0.0006	1
Hepatitis C	1/600000	0.0002	1
HIV	1/800,000	0.0001	1
HTLV I/II	1/250,000–1/2,000,000	0.0004–0.00005	2
Parvovirus B19	1/10,000	0.01	2
Transfusion-associated malaria	Rare		3

1- Busch Mp, Kleinman SH, Nemo GJ. Current and emerging risks of blood transfusions. *JAMA*, 2003; 286:959
2- Goodnough LT, Brecher ME, Kanter MH. Transfusion Medicine. First of two parts. *N Engl J Med* 1999; 340:438
3- Reprinted with permission from Menitove JE. How safe is blood transfusion? In: Smith DM Jr, Dodd RY, eds. *Transfusion-transmitted infections.* Chicago, Ill: ASCP Press; 1991:10. By permission of the American Society of Clinical Pathologists.
[a] Frequency, risk per unit transfused.
AIDS, acquired immunodeficiency syndrome.

result in blood conservation. Use of all modalities that result in blood savings will yield a better result than any single modality. Much of the chapter will be directed toward the cardiac surgery setting, but most of these techniques can be applied to a wide variety of surgical procedures where significant blood loss is anticipated.

AUTOLOGOUS BLOOD SALVAGE

Autologous blood transfusion involves the harvesting of blood or blood products for subsequent administration to the same patient. Autologous transfusion was originally used to secure blood replacement when circumstances made conventional transfusion of banked blood impossible. However, safety has become the driving force behind further development and implementation of autologous transfusion procedures.

The concept of autologous blood transfusion was introduced into medical practice in 1818. Blundell (6) has been credited with performing the first such autotransfusion of blood recovered during postpartum hemorrhage. He also published a series of experiments in which he demonstrated that autologous blood transfusion in

animals with a syringe-infusion technique was safe, minimized air embolism, and was preferable to allogeneic blood transfusion (6). The apparent first instance of transfusion of blood collected intraoperatively was carried out by Duncan in 1885 (7). In that case, a small amount of blood collected from an amputated limb was anticoagulated with sodium phosphate and injected into the patient intravenously. Published in the 1920s and 1930s, a series of small case reports described blood that was collected from various abdominal cavities, strained through sterile gauze, citrated, and then reinfused to the patient. At this time, adverse reactions, including hemoglobinuria, were recognized and documented. Suction apparatuses were eventually used to facilitate the collection of salvaged blood for reinfusion (8). Even in the 1940s, when transfusion-transmitted disease was not an issue, the cost-effectiveness and benefits of autotransfusion were recognized. In 1968, Wilson and Taswell (9) introduced a new apparatus that permitted blood collection, processing, washing, and reinfusion in a continuous process. This development rapidly transformed intraoperative salvage techniques. With the apparatus, blood was collected from the surgical field via a suction aspirator; the blood was then fed into a continuous-flow centrifugation bowl in which the erythrocytes were selectively separated and extracted from the waste supernatant. These washed RBCs were then resuspended for infusion back to the patient. In 1970, Klebanoff (10) introduced a modified disposable autotransfusion apparatus that was considered to be safe, simple, and efficient. Further refinements in the development of washing with intermittent-flow centrifugation devices resulted in a decrease in the coagulopathy associated with intraoperative blood salvage. The removal of thromboplastic material by washing decreased the hemorrhagic complications but also resulted in removing all plasma proteins, including procoagulants (11,12). For safety, contemporary autotransfusion practices rely on a combination of reservoirs for collection and washing procedures.

ACUTE NORMOVOLEMIC HEMODILUTION

ANH is one of the many options clinicians may use to minimize perioperative exposure to allogeneic blood products. ANH is a single term for a broad therapeutic initiative that involves simultaneously removing the patient's whole blood and replacing it with an acellular fluid product. By producing a considerable decrease in the erythrocyte mass and, thus, a decrease in the net erythrocyte loss, ANH often decreases subsequent need for allogeneic blood products. The volume of blood conserved is directly proportional to the differences between the original and postdilution Hct values. These autologous units have a full complement of coagulation factors and platelets, which may limit but not eliminate the development of coagulopathy in those patients in which it is used. The only blood conservation technique that results in fresh whole autologous blood, ANH is endorsed by the National Institutes of Health Consensus Conference on Perioperative Red Blood Cell Transfusion (3) and by the American Society of Anesthesiologists. This accessible and easily institutable technique should be considered for appropriate surgical patients, although its suitability and efficacy will depend on the clinical situation (13,14).

ANH is based on studies conducted in the 1950s that demonstrated well-maintained compensatory responses to acute anemia when up to 50% of the patient's total circulating Hgb mass was removed (15). Further studies on the rheological, hemodynamic, metabolic, and cardiovascular consequences of hemorrhagic shock provided additional support for the concept of hemodilution (16). A 1972 study found that until an Hct value of 30% was reached, decreased viscosity and increased cardiac output (CO) provided maintenance of a maximal oxygen delivery to the tissues during hemodilution (17). In many situations, ANH is considered to be a viable alternative to transfusion with allogeneic blood products (18) and since the early 1970s has been used for surgical patients.

Physiology of ANH

Depending on the amount of blood removed, ANH can produce a rapid and sometimes severe acute anemia. This in itself is the reason for the poor acceptance of the procedure by many clinicians. In fact, compensatory mechanisms in response to ANH are protective to the individual even at hemoglobin levels thought to be consistent with organ and tissue injury (19,20). The compensatory mechanisms in response to ANH include the following:

1. Increased cardiac output.
2. Increased stroke volume.
3. Slight (not clinically significant) increase in heart rate.
4. reduced blood viscosity and therefore decreased after load (systemic vascular resistance).
5. Increased blood flow to oxygen dependent tissues–beyond the CO increase.
6. Increase in oxygen extraction in end organs.
7. Increased coronary blood flow.

Of utmost importance to all clinicians is the fact that tolerance of anemia is as individual as the patient. Therefore, it is pertinent that in addition to understanding the physiology of ANH, one must be vigilant in observing the patient's response to the induced anemia.

Patient Selection Criteria

The criteria for selection of patients for perioperative hemodilution described first by Kreimeier et al. (21) include the following:

1. An estimated blood loss ≥1500 ml;
2. Preoperative hemoglobin concentration ≥12 g per dl after correction of norvolemia.
3. Normal cardiovascular function (i.e., no ischemic signs, no ST segment changes)
4. Absence of restrictive or obstructive lung disease (confirmed by preoperative CXR and possibly lung function tests).
5. Absence of renal disease
6. Absence of untreated hypertension and liver cirrhosis.
7. Absence of coagulation abnormalities
8. Absence of infection.

The above criteria are not standardized and maybe modified as needed. Blood loss could be addressed by including all patients who are typed and crossed for allogeneic blood as part of their preoperative evaluation. Absence of renal lung or other disease is relative indications and need to be evaluated case by case.

Organ Systems Vulnerable to Ischemia During ANH

The controversy for the end point of ANH still exists. The end point of ANH is described in terms of the ending hemoglobin. Removal of whole blood to 9 gm per dl is used by some as an end point for ANH (22).

With the exception of the myocardium, the enhanced cardiac output is distributed to vital organs at approximately the same relative fractions as at a normal hematocrit.

Heart

As the hematocrit is reduced, due to coronary vasodilation and improved blood fluidity, the increase in coronary blood flow is the greatest as compared to other organs. Oxygen delivery to the myocardium remains *adequate* during hemodilution down to a hematocrit of 25% (23). Laxenaire et al. (24) have demonstrated that there is no deterioration of myocardial dipyridamole-thallium scan before and after normovolemic hemodilution in patients with coronary artery disease. Extensive monitoring of patients with limited coronary reserve is pertinent.

Circulatory problems and arrhythmias (atrial fibrillation) can occur at lower hemoglobin levels (25). Patients with an ejection fraction >50 % and untreated coronary ischemia are suited for limited hemodilution before cardiac and noncardiac surgery. This reduced ejection fraction along with reduced afterload and intramural tension is followed by reduced oxygen requirement. Bak et al. (26) have shown that a reduction in hemoglobin to 8.0 g per dl during acute normovolemic hemodilution does not normally compromise systolic or diastolic myocardial function as determined by transesophageal echocardiography. Preload, left ventricular ejection fraction, and cardiac output increase with a concomitant fall in systemic vascular resistance.

Despite the temporary loss of RBCs with ANH, most studies have demonstrated that oxygen delivery is maintained and oxygen extraction is increased during ANH as long as adequate volume and tissue perfusion are maintained (19,27).

Gastrointestinal Tract

Under normal conditions the splanchnic O2 uptake represents 25% of total body consumption. Kleen et al. (28) investigated the effects of ANH on gastric mucosal oxygenation in 16 splenectomized anesthetized beagles who were isovolemically hemodiluted to a hematocrit of 20. Median total gastric mucosal blood flow and mean pHi at baseline and upon ANH did not change significantly. The authors conclude that severe hemodilution to a hematocrit of 20% does not impair gastric mucosal oxygenation and poses no risk to gastric mucosal integrity.

Splanchnic Perfusion

Habler et al. (29) assessed hepatorenal perfusion and function in 22 dogs undergoing acute normovolemic hemodilution (ANH) to a hematocrit (Hct) of 20% using 6% hydroxyethyl starch (200.000 per 0.5) as the diluent. Redistribution of intestinal flow might be the basis for the preservation of tissue oxygenation during moderate isovolemic anemia (29). The authors found that hepatic arterial blood flow increased by 86%, whereas portal perfusion increased by 28%. Small intestinal mucosal perfusion increased by 68% while the non-mucosal tissue compartment of the gut wall received 32% more blood flow after ANH proportional to the increase in cardiac index after ANH.

Effect of ANH on Other Organ Systems

Nervous System

Weiskopf et al. (30) confirmed that acute isovolemic anemia subtly slows human reaction time, degrades memory, increases heart rate, and decreases energy level. They also found that improving arterial oxygen content by administration of added oxygen reversed the subtle cognitive function and memory deficits created by acute severe isovolemic anemia (Hgb concentration of 5 g per dl) in humans.

Previous studies have found subtle slowing of responses in tests of addition and digit-symbol substitution during acute severe isovolemic anemia to a hemoglobin of 5 g per

dl in healthy unmedicated humans. Weiskopf et al. (31) recently demonstrated that Somatosensory evoked potentials (SSEPs) were not negatively affected by acute severe isovolemic anemia.

Pulmonary

Hemodilution in patients with acute or chronic pulmonary disease is still debated as the most important prerequisite of hemodilution is adequate oxygenation of RBC hemoglobin during passage through pulmonary vascular bed. This is disputed as improvement of blood fluidity concurrent with hemodilution may enhance the capillary blood flow. On the other hand, enhanced pulmonary perfusion in the presence of unchanged ventilation leads to ventilation-perfusion mismatch, which in turn will reduce the oxygen content of arterial blood.

Boldt et al. (32) in a randomized study compared the effects of acute normovolemic HD (n = 15) using hydroxyethyl starch solution (HES) on extravascular lung water (EVLW) with those of an untreated control group (n = 15) of cardiac surgery patients submitted to extracorporeal circulation (ECC). A thermal-dye technique was used to measure EVLW. The authors found that preoperative normovolemic HD did not increase lung water content significantly nor compromise pulmonary function even in cardiac surgery patients. Although ECC provides an additional HD (crystalloid priming of the heart-lung bypass machine) and possibly damage of capillary integrity, the two groups did not differ.

Retina

The retinal vasculature is capable of autoregulatory vasoconstriction or vasodilatation to maintain relatively constant retinal tissue PO_2 (P_rO_2) (33). ANH was found to cause an initial increase in (P_rO_2) in cats and then decreased after further Normovolemic Hemodilution. An increase in erythrocyte flux in the retinal capillaries during hemodilution explains the high retinal P_rO_2 and may have overruled any autoregulation. The initial increase in P_rO_2 may contribute to the reported therapeutic efficacy of limited isovolemic hemodilution in central retinal vein occlusive diseases (34).

Optic Nerve Head

Hemodilution leads to an increase of PO_2 (vitreous) reflecting a similar rise of the optic nerve head (ONH) tissue PO_2. This effect results from an enhanced blood perfusion of the ONH, which overcompensates the decrease of blood O_2 content (35).

Effect of Anesthesia on ANH

Weiskopf et al. (19) studied the response of hemodilution to a Hct of 30% in 20 patients anesthetized with fentanyl, nitrous oxide and enflurane. Anesthesia decreased stroke volume, cardiac index, oxygen delivery and consumption. Mild hemodilution did not further decrease oxygen delivery and did not change oxygen consumption and blood lactate concentration. Thus, critical oxygen delivery was not reached in patients with ANH to Hct of 30%.

Recently, Ickx et al. (36) studied the response to moderate hemodilution (Hgb 8 g per dL) in patients awake and anesthetized with fentanyl, nitrous oxide, and isoflurane. The maintenance of adequate tissue oxygenation during acute anemia depended on an increase in both cardiac output and tissue oxygen extraction. In the awake group, ANH resulted in a significant increase in cardiac index, and was related to both an increase in heart rate and stroke index. Oxygen delivery remained unchanged, but oxygen consumption increased significantly, resulting in an increase in oxygen extraction ratio. In the anesthetized group, ANH resulted in a significantly smaller increase in cardiac index and was related solely to an increase in stroke index. Oxygen delivery decreased but oxygen consumption was maintained as oxygen extraction increased. Anesthesia significantly reduces the cardiac output response associated with ANH. This could be related to the effects of the anesthetic drugs on the autonomic and the cardiovascular systems (36).

Monitoring During ANH

Adequate monitoring of cardiopulmonary parameters is pivotal in maintaining tissue oxygenation in ANH. Vital sign monitoring is routine and a standard practice as under any form of anesthesia. Application of standard anesthesia monitoring is required. More invasive monitors can always be added depending on the complexity of the surgical procedure, the patient's comorbidity and the clinician's discretion. All efforts are directed at maintaining adequate intravascular volume. Patients with valvular heart disease present a more complex problem, and should have invasive monitoring and/or ongoing transespohageal echocardiography (TEE). Introduction of ANH in these circumstances is associated with difficulty and complexity. There is no current noninvasive monitor that enables the clinician to accurately assess oxygen deficit or oxygen delivery affecting oxygen utilization.

Procedure Description

ANH is characterized as either moderate or severe hemodilution, depending on whether the Hct is 25% to 30% (moderate or limited) or 15% to 20% (severe or extreme). ANH is not simply the administration of nonblood fluid to reduce the Hgb but involves the active withdrawal of the patient's blood and the temporary acceptance of a lower Hgb. The collected blood is temporarily stored properly

labeled (see AABB guidelines) and subsequently transfused to the patient when indicated. Severe hemodilution, which may result in significant hemodynamic and physiological compromise that necessitates careful patient monitoring, may be most suitable for patients undergoing the protective effects of hypothermia and extracorporeal circulation.

Before the withdrawal of blood, adequate intravenous access is necessary. A urinary catheter, pulse oximeter for continuous monitoring of Hgb saturation, and an intra-arterial catheter should be in place. Some authors have advocated the use of a central venous catheter (37) or pulmonary artery catheter for assessing ventricular filling (38) or approximating the adequacy of tissue oxygenation (39).

The hemodynamic response to phlebotomy of 500 to 700 mL is often minimal, and larger volumes of 1,000 to 2,000 mL have been removed without difficulty (40) but are more likely to elicit a stress response and or hypotension (41). Blood, which is usually withdrawn from a central venous or arterial catheter, drains by gravity into standard blood collection bags containing an anticoagulant such as ACD-A or citratephosphate-dextrose. If the blood is drawn from a peripheral vein, an automated blood pressure cuff may facilitate collection. If the patient requires CPB (Cardiopulmonary bypass), the blood may be collected before or after heparin exposure (42,43). Blood that is exposed to heparin may have a weaker hemostatic effect due to the effect of heparin on platelet function (44).

The collection of fresh whole blood should require about 10 minutes per unit. Strict adherence to sterile technique should be maintained. The blood collected must remain in the presence of the patient and should not leave the operating room so that there is little chance of administering it to the wrong patient. The blood should remain at room temperature in the operating room; if removed from the operating room, it must be appropriately labeled and stored at 4°C to 6°C (see AABB guidelines) (45). The blood should be readministered in reverse order of collection, a method that ensures that the most hemodiluted unit is given first and the one with the most clotting factors and RBCs will be given last (46).

Calculating Blood Withdrawal

The amount of blood withdrawn for ANH, usually between 400 and 2,000 mL, depends on the anticipated surgical blood loss and the patient's initial Hgb (43,47,48) and may be determined as a percentage of estimated blood volume or body weight. ANH has usually been limited to 20 mL per kg in children (49). In adults, the Hgb will decrease approximately 1 g per dL for each unit of blood removed.

Various formulae and nomograms have been proposed to determine the amount of blood that should be reached to reach the desired hematocrit. To achieve a higher probability of avoiding allogeneic blood transfusions one must attain a low hemoglobin level after ANH. The correct prediction of estimated blood volume (EBV) is important, particularly in extreme hemodilution. At lower levels, the margin of safety to ensure adequate tissue oxygenation is narrow. Performing ANH beyond the targeted critical hemoglobin as a result of overestimation of EBV can expose patient to the risk of tissue hypoxia.

There are several formulas to guide the process of withdrawing the predetermined amount of blood: $V = EBV \times Hct_i - Hct_f/\text{average Hct}$, where the average $Hct = (Hct_i - Hct_f)/2 + Hct_f$, where EBV is the estimated blood volume, V is the volume to be collected, Hct_i is the initial Hct, and Hct_f is the final desired Hct. An alternate formula that is an accurate guide to determine the volume of blood to withdraw for ANH is $V = EBV\ (Hct_i - Hct_f)\ (3 - \text{avg Hct})$.

The formula by Bourke et al. (49a) is reported to overestimate EBV 60% to 70 ml per kg in the adult. The overestimation leads to lower hemoglobin than targeted, a fact that may endanger the patient. The new iterative model proposed by Meier et al. (50) predicts EBV more reliably, is physiologically based and leads to an improvement in patient safety.

During ANH, large amounts of fluid are frequently necessary to maintain normovolemia, although the net fluid increase may be insignificant compared with the usual transfusion requirements (43). Complications associated with the increased fluid include peripheral edema, pulmonary edema, abnormal wound healing, and worsened postoperative pulmonary function (51). Peripheral edema is relatively common with crystalloid replacement during ANH, but pulmonary edema is fortunately not common (38). In most patients with good ventricular function, the increased fluid is well tolerated and usually resolves in 72 hours. Left ventricular hypertrophy or dysfunction reduces the tolerance to the increased fluid volumes. Overall, the benefit of ANH appears to outweigh the problems of the increased intravascular fluid (52).

Because the withdrawn blood must be adequately replaced with crystalloid or colloid fluid, (43) comparisons have been performed to determine the optimal type of fluid replacement for ANH. Although crystalloid alone is acceptable, either colloid alone or a combination of crystalloid and colloid is favored (53). Albumin, (53) hydroxyethyl starch, and dextran are all colloids that have been successfully used for ANH (54). Dextran provides excellent volume replacement but may cause greater blood loss in certain situations because of alterations in coagulation function (54). As such, dextran should be avoided in cardiac operations

(55). Abnormal clotting studies may be seen with hydroxyethyl starch usage, but clinical bleeding has not yet been proven to be associated with this colloid.

Crystalloid is usually given as a 3 to 4 mL replacement per mL of withdrawn blood; colloid is usually given at 1 to 2 mL per mL of blood withdrawn. Generalized edema is more common with crystalloid than colloid replacement. Colloids have better intravascular retention and are more effective in restoring normovolemia than are crystalloids at four times the volume (58). Colloids are also associated with greater hemodynamic stability. Intravascular crystalloid equilibrates quickly with the interstitial spaces. Only a small volume of crystalloid remains in the intravascular space with the heart and gastrointestinal tract developing the most edema (57).

The primary indication for ANH in surgical patients is the reduction of allogeneic blood transfusion. Perioperative transfusion of RBC (47,58–61) and other blood products (62,63) have been decreased with ANH. As important, the percentage of patients who do not receive any blood products is increased from 13% to 42% if ANH is combined with other blood salvage procedures during cardiac (64) and noncardiac operations (47).

ANH may be used in any type of operative procedure, including emergency procedures, if the patient is hemodynamically stable. In contrast to preoperative donation, infection does not preclude the use of ANH. The stress response is different during blood withdrawal in the awake patient for preoperative donation than it is during ANH in the anesthetized patient (41). Intraoperative ANH is not stress inducing; hormonal markers for stress are not elevated (41). However, preoperative blood donation has resulted in significant hemodynamic fluctuations in elderly patients, leading to more urgent cardiac operations and, perhaps, contributing to perioperative morbidity (65). With intraoperative ANH, invasive and noninvasive hemodynamic monitoring is available. These factors may increase the safety of intraoperative ANH and permit the participation of higher risk patients who would be otherwise rejected for preoperative donation (41). Because intraoperative ANH may be as effective as preoperative donation in reducing blood transfusions (66), ANH may be considered when preoperative blood donation is questionable, unsuitable, unavailable, or urgent.

Safety and Physiological Implications of ANH

Since ANH was introduced, studies have been performed to determine its benefits and risks (40). Unfortunately, no consensus has been established about the safety of ANH. Many physicians support the use of moderate hemodilution (38) yet consider the risks associated with an Hct less than 28% too great. The safety of ANH appears to be a function of various factors that are unique for each patient.

The safety of ANH has been demonstrated in cardiac, (55,61) vascular, (47) orthopedic, (63,67) urological, (66) and general operations (68). In a well controlled prospective study involving patients undergoing radical retropubic prostatectomy, ANH was recently determined to be safe and beneficial. An expected blood loss of 1,000 mL in this study was associated with the greatest benefit in reducing allogeneic blood transfusion (38). This degree of blood loss may be a good indication for ANH but has not been validated.

Contraindications to Performing ANH

Certain factors increase the risk of hemodilution, and ANH may not be suitable for some patients. In the absence of agreed upon standards, the author takes the position that all patients can be candidates for ANH. Important mitigating factors that are of concern and be possible contraindications include:

1. Anemia with hemoglobin <7.0 grams.
2. Hemoglobinopathy associated with hemolysis (SS disease, etc.). The procedure itself is not a contraindication but data on RBC survivability at room temperature is not known.
3. Active Ischemic Cardiac disease (severe aortic stenosis, unstable angina, or both), these patients can tolerate moderate amounts of ANH without difficulty if their cardiac ischemia is adequately treated.
4. Renal failure—ANH can be performed with the aid of continuous veno–veno hemofiltration.
5. Known coagulopathy (low plasma-coagulation proteins) (46) associated with active bleeding.
6. Severe chronic obstructive pulmonary disease (if the baseline oxygenation is significantly impaired) (46).

Coronary Artery Disease (CAD) and ANH

The indications and consequences of ANH in the patient with coronary artery disease (CAD) for cardiac or noncardiac operations are not clear. The safety of ANH in patients with ischemic heart disease has been questioned recently in light of its potential benefit (69). Numerous animal and human studies concerning CAD and ANH have produced conflicting data. CAD and myocardial dysfunction are probably the two most important factors concerning the safety of ANH.

Johnson et al. (61) studied patients undergoing CABG and ANH and targeted an Hct of 32% or 25% for transfusion. They found no differences between these groups in fluid requirements, hemodynamic profile, or perioperative complications. They were also unable to identify an

increased risk associated with a lower Hct in patients with good ventricular function who underwent elective CABG. However, the patient population was not large, and the study will need to be confirmed. In another series of patients undergoing CABG and hemodilution to an Hct of 15%, there was no evidence of myocardial ischemia or inadequate tissue oxygenation (70). Moreover, compared with patients who did not undergo ANH, those who had hemodilution had improved tissue oxygenation before CPB. Recently, patients hemodiluted to 15% before CABG by withdrawal of 1,500 mL of blood subsequently had their Hct raised to 20% and then 25% (71). Electrocardiographic or metabolic data at any of the Hct levels did not show evidence of ischemia. In contrast, Weisel et al. (58) looked at myocardial metabolic indices in patients for CABG operations who were hemodiluted to an Hct of 21% to 24%. They reported delayed myocardial metabolic recovery, yet no mortality, myocardial ischemia or difference in creatinine kinase MB isoenzymes between hemodiluted and control patients. In this study, it is important to note that this delayed metabolic recovery was present long after the metabolic-reducing effects of general anesthesia. The assessment of these patients focused primarily on postoperative risk and hemodilution. Kim et al. (72) did not find postoperative evidence of insufficient myocardial or systemic oxygen supply in patients hemodiluted to an Hct of 23%. These patients had good myocardial baseline function and increased their CO without difficulty.

The use of moderate ANH is safe in noncardiac operations such as aortic-aneurysmal repair (47,73). Kramer et al. (47) saw no evidence of tissue hypoxia based on the mixed venous oxygen saturation in patients undergoing abdominal aortic operations. Recently, a study using transesophageal echocardiography, a more sensitive indicator of myocardial ischemia, in patients undergoing abdominal-aortic-aneurysm repair with ANH to an Hct of 30% (74) showed no evidence of segmental regional wall motion abnormalities during aortic cross-clamping. These patients with CAD not only tolerated ANH but also had a decreased incidence of myocardial ischemia. Patients undergoing general operations appear to tolerate an Hct of 25% if the left ventricular function is adequate and CAD is not too severe. In contrast, others have found evidence of myocardial ischemia in patients undergoing vascular operations who had a postoperative Hct less than 30% after ANH (75,76) . Some people believe that patients with vascular operations should not undergo ANH because of their high incidence of CAD (53). Concern regarding myocardial injury is valid because anemia may predispose a patient to ischemic injury (58). The mechanism of myocardial ischemia may be a result of the reduced oxygen-carrying capacity (anemia) and the compensatory mechanisms (i.e., tachycardia) that increase myocardial oxygen consumption (20).

Studies in animal models of CAD and ANH have also yielded conflicting results. As Hct is reduced from 43% to 20%, myocardial oxygen demand is greatly increased (20). Below an Hct of 15%, the myocardium is unable to extract further oxygen (77) or increase coronary blood flow enough to satisfy additional oxygen demands. If the heart is unable to increase or maintain CO, and thus coronary perfusion, myocardial ischemia will result.

The consequences of hemodilution in animals or humans with compromised coronary blood flow are not fully appreciated. The pressure gradient across a stenotic artery is a critical determinant of myocardial ischemia. Increased coronary blood flow secondary to hemodilution may increase turbulence that results in a pressure decrease proximal to the coronary stenosis. Because these coronary vessels may be maximally dilated, they are unable to further compensate, which results in a reduced gradient and reduced coronary blood flow distal to the stenosis (78). Therefore, the expected increase in coronary blood flow associated with hemodilution may not occur in stenosed coronary arteries (76,78). Hemodilution that would normally have increased coronary blood flow by 200% may increase coronary blood flow by only 47% in stenotic arteries (79).

Another potential cause for myocardial ischemia in the patient with ANH and CAD is the distribution of coronary blood flow. Under normal circumstances, endocardial coronary blood flow is slightly greater than epicardial coronary blood flow. With mild hemodilution, the ratio of endocardial to epicardial flow is maintained (20). In two studies, (81,88) electrocardiographic changes and myocardial failure resulted when dogs were hemodiluted. The maintenance of myocardial oxygenation is dependent on adequate perfusion pressure, particularly when the Hct is low (82). Data by Crystal and Salem (82) suggest that myocardial dysfunction occurs with a higher perfusion pressure in the presence of CAD and even moderate hemodilution. Heart failure occurred at a higher Hct in dogs with stenosed coronaries, and has lead some to suggest that patients with CAD have less reserve and may require a higher Hct than the same cohort with normal coronaries.

Spahn et al. (83) found the lowest Hgb without myocardial dysfunction was 7.5 g per dL in dogs with artificially created left anterior descending coronary artery stenosis. The coronary stenosis limited the increase in coronary blood flow that usually follows hemodilution. Perhaps more important is that regional myocardial dysfunction was reversed with blood transfusion or removal of coronary constrictions. In addition, the mechanism of arthrosclerosis is different than that of mechanical obstruction.

Some animal studies have refuted previous investigations of ANH in CAD models. When Yoshikawa et al. (84) occluded the coronary arteries of dogs during ANH, hemodilution did not worsen ischemia. More recently, dogs

hemodiluted to 15% significantly increased coronary blood flow across a stenotic portion of left anterior descending artery (LAD) (78). A large increase in coronary blood flow despite coronary stenosis may explain a lack of morbidity and mortality in many patients who undergo ANH and have CAD. Coronary blood flow in humans has been measured through cannulation of the coronary sinus after hemodilution from an Hct of 37% to 28%. The coronary blood flow increased 59%, and there was no evidence of increased oxygen extraction by the myocardium (85).

The degree of anemia that a patient with CAD can accept is not clear, but the minimal Hgb for sufficient myocardial oxygen supply in a patient with CAD will depend on myocardial oxygen demand. If the coronary blood flow is unable to increase in response to myocardial oxygen demands as the Hct decreases, this is the minimal safe Hct for hemodilution. Some studies suggest that a specific Hct is intolerable; however, tachycardia and decreased coronary driving pressure are important factors and may account for an insufficient balance of myocardial oxygen supply and demand. Patients are frequently hemodiluted to an Hct of 20% at the onset of CPB without widespread morbidity and mortality. Tolerance of a low Hct is quite different during CPB than it is in patients undergoing noncardiac operations.

Because many studies have been unable to reach a conclusion concerning CAD and ANH, some researchers maintain that coronary disease is a relative contraindication to ANH and suggest maintaining an Hct of 30% to achieve optimal myocardial recovery (86). Others will exclude the patient with CAD from ANH if the patient has depressed left ventricular function because that patient may require a higher Hct to avoid ischemia (87). Patients with cardiovascular disease are known to have episodes of silent ischemia. More important is that a certain percentage of patients not considered at risk for CAD have evidence of silent myocardial ischemia that places them at risk. Some people consider this sufficient evidence to argue against the routine use of ANH. As yet, no successful method identifies patients who will be at increased risk for myocardial ischemia with ANH. A patient should be assessed carefully and a determination made as to the benefit and potential risk of ANH based on the degree of hemodilution, ventricular function, and possibility or severity of CAD.

Other Factors Limiting the Degree of Hemodilution

a. Age

The age of a patient may also limit the degree of hemodilution. Severe hemodilution is usually reserved for younger patients. An Hct of 15% to 20% is well tolerated in a young healthy patient during cardiac or noncardiac operations (63,67,68). ANH has been used in children for major cancer operations, liver resections, and cardiac operations (49,88). Hemodilution to an Hct of 20% is safe in humans (63).

Many elderly patients tolerate ANH quite well (54). When patients with a mean age of 69 years undergoing major operations with ANH were compared with a group of patients with a mean age of 46 years undergoing major operations, the perioperative outcomes were similar (89). With ANH, the hemodynamic compensatory actions of patients above 60 years of age were similar to those of patients less than 60 years of age (90). Although a patient's age may partially limit the response of compensatory mechanisms to hemodilution, many elderly patients respond effectively to the volume shifts of phlebotomy (91). ANH is generally considered as safe in patients greater than 60 years of age as in those less than 60 years of age. Although the inability of some geriatric patients to increase myocardial blood flow with extreme hemodilution is well documented, (63,65) extremes of age are not contraindications to ANH (56). Older patients may require an Hct greater than 30%, particularly in the postoperative period when anesthesia no longer reduces metabolic oxygen requirements (39).

b. Degree of acceptance of low hematocrit

Animal studies support the finding that the limit of hemodilution for physiological integrity appears to be an Hct of 10% (79,92). Hcts of 10% have been documented during cardiac operations in children with congenital heart disease who were Jehovah's Witnesses. These children displayed no evidence of neurological sequelae or other complications attributable to hemodilution (49,92).

Compensatory Mechanisms in ANH

The major limiting factor in the tolerance of a low Hct is oxygen demand. The removal of blood causes a reduction in arterial oxygen content ($Ca0_2$). Despite the reduction in oxygen content with a low Hgb, oxygen consumption in humans is such that there is a large margin of safety (20). When oxygen delivery remains sufficient, compensatory mechanisms for anemia are not invoked. Cerebral and myocardial tissues are more vulnerable to reduced oxygen-carrying capacity because they have high oxygen utilization. If oxygen supply is inadequate, compensatory mechanisms will attempt to increase oxygen delivery by increasing perfusion (39).

The major acute compensatory mechanism for maintenance of oxygen delivery during ANH is an increase in CO, (91) which increases in direct proportion to a decrease in Hct (39). The increase in CO is primarily due to increased stroke volume (20,37,68) and increased venous return (89). The hemodiluted blood is less viscous; therefore, afterload is reduced and venous return increased (54).

For these compensatory mechanisms to maintain systemic oxygen transport, normovolemia and adequate cardiovascular function are necessary. Compounding intraoperative factors such as hypovolemia, general

anesthesia, or hypothermia may limit compensatory increases in CO (63). If the CO is unable to increase in response to hemodilution and decreased arterial oxygen content, increased oxygen extraction is another compensatory mechanism (93).

During ANH, a widening arteriovenous oxygen saturation difference (63) or increased heart rate (89) may indicate that oxygen delivery is marginal or inadequate. An increased heart rate during anesthesia may be a sign of hypovolemia, although tachycardia is not a completely reliable indicator (78). In a patient's awake state, heart rate will increase with blood withdrawal to augment CO; conversely, in the anesthetized state, the stroke volume will increase (94).

Hemodilution also changes the distribution of blood flow between and within organs. Within a certain range of Hct levels, a constant rate of oxygen delivery will be maintained to vascular beds by vasodilation and vasoconstriction depending on the blood viscosity and oxygen consumption (77). Blood flow to tissues and organs that are supply-dependent, such as the heart and brain, increases significantly with hemodilution to an Hct of 15% (20,78). These tissues use the greatest amounts of oxygen and have a high near-maximal oxygen-extraction ratio. They are unable to compensate for hemodilution-induced, reduced oxygen delivery by increasing oxygen extraction. Cerebral blood flow increases 500% to 600% in both animals and humans with hemodilution to an Hct of 10% (20). This increase in cerebral and myocardial blood flow is primarily related to the change in viscosity, but is not in the same proportion as the increase in CO. During hypothermia, patients may have higher cerebral oxygen delivery with a 23% Hct than a 28% Hct (95). In fact, Lilleaasen (96) has shown that during CPB, cerebral circulation is maintained as well at an Hct of 18% as at 27%.

Blood flow to the rest of the body is more reflective of the change in CO associated with hemodilution. Blood flow in the vertebral artery, mesenteric artery, and lower aorta matches the change in CO. Direct measurements of oxygen tension in these tissues have shown adequate oxygenation with an Hct of 20%. Blood flow in the hepatic and carotid arteries increased proportionately less (39). In dogs undergoing ANH, renal blood flow remains stable, (97) and in patients undergoing aortic vascular reconstruction, renal function may even be preserved (60).

ANH not only results in alteration in oxygen-carrying capacity but may also challenge osmotic and intravascular-interstitial fluid balance. The lungs are at risk for interstitial or frank pulmonary edema with ANH because these patients receive significant fluid challenges. Most patients will exhibit some increase in lung water after CPB, but hemodiluted patients have even more of an increase. Diuretics, fluid restriction, or both can serve to remove this fluid more rapidly, although it may resolve within the first 4 days (52). If the patient receiving crystalloid is supplemented with some colloid to increase intravascular oncotic pressure, renal blood flow is augmented and contributes to more rapid diuresis (60).

The Colloid-Crystalloid Controversy

Maintaining colloid osmotic pressure during CPB is an important factor in reducing postoperative pulmonary dysfunction (98). Several studies have attempted to determine if the choice of colloid or crystalloid influenced pulmonary dysfunction after CPB with ANH. Compared with patients given crystalloid, patients given colloid tended to have reduced pulmonary complications (98). The use of crystalloid solutions to prime the extracorporeal circuit or replace blood during ANH increases the alveolar-arterial oxygen gradient after CPB (98). If a colloid is used for ANH in patients undergoing CABG, lung water and the pulmonary gas exchange are no different than those in patients who did not undergo ANH (100). With crystalloid compared with colloid use in CABG patients, there is also a greater alveolar-arterial gradient upon extubation (58). Yet others have found no adverse effects after infusing 10 L of crystalloid, (94) and some patients undergoing extreme hemodilution tolerate the fluid challenges without developing pulmonary edema (98).

Hypertonic solutions have been used for ANH. Boldt et al. (55) found that a hypertonic hydroxyethyl starch solution was more effective in preserving pulmonary gas exchange, maintaining adequate circulatory volume, and preserving hemodynamics in CABG patients undergoing ANH. The effects of hypertonic solutions on hemodynamic parameters during ANH are not transitory, (55) and renal blood flow is well maintained. However, it is important to be aware of the potential complications of hypertonic solutions such as hypernatremia and central pontine myelinolysis.

The physiological implications of ANH are different for each patient. The clinician must be aware of the potential for physiological insult with moderate or severe hemodilution and apply that knowledge to the care and monitoring of each specific patient. In contrast to preoperative blood donation, the procedure of ANH is begun after the induction of anesthesia; therefore, the patient is continuously monitored.

Risk of Recurarization During ANH

In clinical practice, ANH is often performed immediately after induction of anesthesia. Therefore, drugs given during induction of anesthesia will be found in the removed blood at similar concentrations to the blood at the moment of removal. Consequently, neuromuscular blocking agents

(NMBAs) as part of an induction regimen, may be found in the removed blood, inducing a certain risk of recurarization during retransfusion.

Efficacy in Reducing Transfusion Requirements

The blood-saving effect of ANH is attributed to several factors. A major reason is the conservation of RBC mass by decreasing the Hct of shed blood. In a patient with an Hct of 40% and an estimated surgical blood loss of 1,000 mL, the RBC loss is 400 mL. If the Hct is only 25%, the RBC loss is reduced to 250 mL. The net RBC mass conservation in this example is 150 mL, which could be even more because a patient's Hct constantly changes during hemodilution (69).

Another explanation for reduced blood product transfusions in cardiac operations with ANH has been credited to a lack of exposure of the withdrawn blood (platelets and coagulation factors) to the deleterious effects of CPB (99). Fresh whole blood collected before CPB improves hemostasis after CPB better than platelet concentrates (100). The hemostatic benefit of a single unit of fresh whole blood has been compared with an allogeneic transfusion of 10 units of platelet concentrates (101). Platelets in fresh whole blood are larger and more hemostatically active (102). Fresh whole blood also contains some clotting factors that may contribute to hemostasis. Autologous fresh whole blood does not undergo certain biochemical processes to the same extent that stored blood does. In contrast to preoperatively donated blood, the fresh whole blood of ANH is stored only briefly at room temperature, a factor that preserves platelet function better than hypothermic storage does.

ANH was used early in the development of cardiac operations because transfusion and excessive blood loss were frequent (103). More recently, ANH is commonly used in many different surgical settings (54). In 1957, Derbyshire et al. (42) were one of the first groups to collect heparinized blood intraoperatively and reinfuse it after CPB. ANH has subsequently been shown to reduce allogeneic blood requirements by 25% to 58% (43,52,61). Recently, Ikeda et al., (104) using multiple blood conservation techniques but not pharmacological hemostatic agents or preoperative donation, found a clear difference in the quantity of intraoperative and postoperative blood products transfused in patients who underwent ANH before CPB. ANH is also popular in spinal operations and joint arthroplasty where it reduces allogeneic blood use (38). In a wide range of surgical procedures, ANH has decreased allogeneic transfusion by 185 to 90% (38). Comparisons of blood use between ANH and historical control subjects reveal a 75% reduction in allogeneic blood use in pediatric spinal fusion, (29) hepatic resection, (105) major colon operations, and radical cystectomy (94). However, as we point out in our discussion, studies in which a therapeutic intervention is compared with historic control subjects are flawed and must be interpreted with great caution.

In 1977, Lilleaasen (96) found that compared with moderate hemodilution, extreme hemodilution further reduced blood loss and transfusion requirements. A recent report from Dale et al. (106) confirms these findings. Dramatic reductions in blood transfusion are also reported with severe hemodilution in settings apart from cardiac operations. Martin and Ott (63) prospectively studied 26 teenagers undergoing Harrington-rod instrumentation for scoliosis who were hemodiluted to an Hct of 15%. Mean allogeneic transfusion requirements were reduced from 4,370 to 750 mL, and, at discharge, total allogeneic blood transfusion in control patients was six times higher than in ANH patients.

Other studies have not found a difference in transfusion requirements with ANH (48,107). Vedrinne et al. (107) compared the hemostatic effects of ANH with aprotinin, which significantly reduces transfusion requirements and blood loss in cardiac operations. Compared with aprotinin, ANH did not reduce transfusion requirements or mediastinal blood loss. The lack of efficacy was postulated as inadequate storage of the fresh whole blood or insufficient volume of blood withdrawn. Vedrinne et al. (48) collected only 400 mL of blood; other ANH studies collected 700 to 1,500 ml, of blood and reported a benefit (43,109). However, Scott et al. (52) withdrew only 575 mL of blood and reported a reduction in blood transfusion in primary cardiac operations. In a noncardiac surgery setting, a case study analysis of patients undergoing radical prostatectomy demonstrated that the blood conservation benefit of ANH was minimal (107). However, the degree of hemodilution in this study by Goodnough, et al. (107) was much less than in other successful trials of ANH. In this trial, dextran, which may adversely affect thrombosis and surgical blood loss, was used as the volume replacement after the blood was withdrawn.

Additional Benefits and Concerns

Other additional benefits of ANH include a reduced incidence of wound infection, (110) an improvement in oxygen delivery to peripheral tissues, and an increase in 2,3-diphosphoglycerate (DPG) (111). Another advantage of ANH over preoperatively donated blood is the fact that ATP and 2,3DPG are decreased in preoperatively donated blood during hypothermic storage. Once transfused, this preoperatively stored blood does not immediately have the same oxygen delivery capabilities as fresh whole blood collected for ANH.

ANH also improves perfusion and oxygen delivery to the tissues by decreasing blood viscosity. With hemodilution to an Hct of 15%, blood acts like a Newtonian fluid (20). The effect of Hct is greatest at a lower flow rate. At a high flow rate, only an Hct of 40% to 45% provides optimal oxygenation (54). At a lower flow rate, an Hct of 45% will reduce oxygen transport as a result of the increased viscosity (54). This, then, is the reason that a lower Hct with lower flow rates can still provide adequate oxygenation.

Hemodilution also affects the shear rate (velocity gradient) of the fluid in the microcirculation. Shear rate varies directly with vessel size; the microcirculation has a low shear rate. At a low shear rate, one sees the maximal effect of lowered viscosity and hemodilution in the capillaries and the postcapillary venules. This low rate results in more homogenous flow that provides better perfusion and reduces the chance of anaerobic metabolism (37,70). In some models, oxygen delivery increases as the Hct decreases to 25% (20). Even with an Hct of 20% during ANH, oxygen transport is reduced only 10% from its maximal value, yet the mean tissue $P0_2$ actually increases slightly. These studies illustrate how ANH increases oxygen supply to the tissues (89). Initiation of hemodilution in tissues that are ischemic results in an increase in oxygen tension (20). Thus, there are numerous theoretical benefits to ANH.

Some clinicians and scientists express concern regarding increased bleeding as a result of hemodilution. However, compared with control subjects, ANH patients undergoing total hip arthroplasty had no increase in surgical bleeding (112). Another concern involves further hemodilution of coagulation factors and thrombocytopenia, but an association of increased bleeding with ANH has yet to be documented. Clotting factors remain within physiological ranges (113).

Adjuncts to ANH

ANH may be combined with other techniques to reduce blood loss.

1. Preoperative Autologous donation (PAD)

Oishi et al. (114) studied 33 patients undergoing total hip arthroplasty [assigned randomly to one of two groups (control, n = 16; hemodilution, n = 17)], to determine the blood transfusion savings if ANH is used in combination with autologous predonated blood and cell saver. Only 41% of the patients in the hemodilution group required any autologous blood transfusion as compared with 75% of the control group. In addition, the hemodilution group required a mean lower quantity of autologous blood transfusion (41% of the estimated blood loss) as compared with the control group (71%). Hemodilution resulted in fewer patients needing autologous predonated blood transfusions. The major benefit of hemodilution was seen when predonation was not possible.

Monk et al. (115) conclude that ANH can replace PAD as an autologous blood option because it is less costly and equally effective. A combination of ANH and PAD can further decrease allogeneic blood exposure, but it increases transfusion costs and wastage. ANH alone resulted in a 21% ABT rate and contributed a mean net savings of 112 mL RBC in blood conservation (equivalent to 0.6 unit of blood). The addition of one or two units of PAD-reduced allogeneic exposure rates to 6% or 0%, respectively. Overall, patients who predonated blood had a mean net loss of 198 mL of RBC (equivalent to one blood unit), due to both an absence in compensatory erythropoiesis and to the wastage of 60% of the blood units donated. Patients who underwent ANH alone had a 60% reduction in mean total transfusion costs ($103 +/− $102) compared with patients who predeposited two units of autologous blood in addition to ANH ($269 +/− $11, $P < 0.05$).

2. Induced Hypotension

Induced hypotension has been combined with ANH to safely reduce bleeding and transfusion requirements (112). Recently, 119 patients undergoing spinal fusion were hemodiluted to an Hct of 20%, hypotension was induced with nitroglycerin, and tissue perfusion remained adequate (67). The drug of choice for induced hypotension with ANH is unclear. Adenosine may provide safe and effective induced hypotension (116). Nitroprusside can also be used but is not universally recommended (97).

3. Mild Hypothermia

Koehntop et al. (117) report that intraoperative mild hypothermia may be advantageous in providing substantial central nervous system and myocardial protection during severe anemia. Lowering body temperature 2°C or 3°C reduces overall oxygen consumption and cerebral metabolic rate by 12% to 20% (Fig. 34.1). This may have therapeutic potential when unintentional, extreme hemodilution suddenly occurs secondary to massive surgical blood loss.

Cost-effectiveness of ANH

ANH is less costly than preoperative autologous blood donation. The autologous units removed during ANH are retransfused before leaving the operating room and therefore require no inventory or testing costs. This in turn, eliminates the possibility of an administrative error that could have led to a mismatch transfusion. The indirect costs associated with PAD such as patient time lost in terms of loss of work, transportation account for reduction in costs associated with the procedure. In addition, the waste of blood

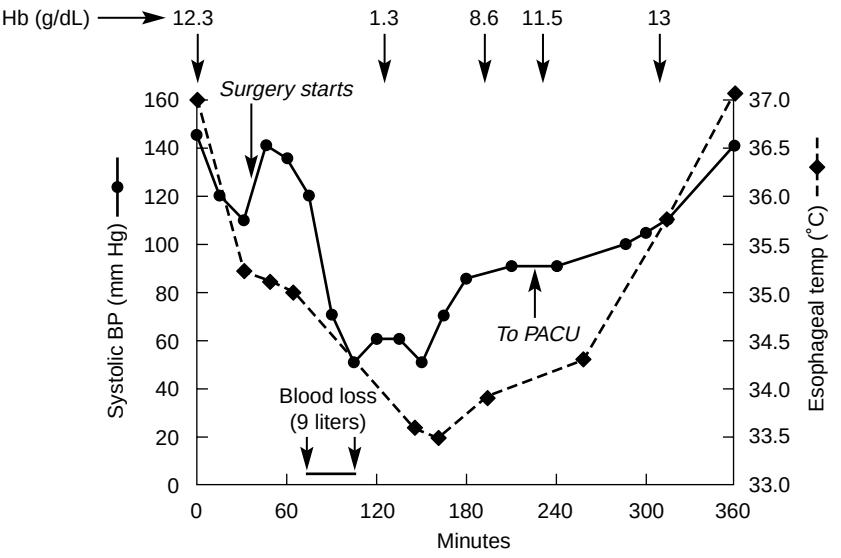

Figure 34.1 Serial changes in esophageal temperature and systolic blood pressure before, during, and after massive surgical blood loss resulting in hemoglobin nadir of 1.3 g per dl. Esophageal temperature was between 35.5°C and 33.5°C intraoperatively. (Adapted with permission from Koehntop DE, Belani KG. Acute severe hemodilution to a hemoglobin of 1.3 g/dl tolerated in the presence of mild hypothermia. *Anesthesiology.* 1999;90(6):1798–1799.)

associated with PAD is completely avoided with this procedure. Because of these advantages, two studies report that moderate ANH is more cost-effective than PAD in patients undergoing radical prostatectomy (115,118).

In summary, a conclusive statement regarding transfusion requirements and blood loss with ANH is difficult. Because multiple conservation techniques are frequently used, the impact of an individual technique is difficult to ascertain. The effect of ANH on transfusion requirements varies greatly depending on the surgical procedure and study design. Many factors contribute to perioperative transfusion and blood loss (13). The number of blood products transfused is strongly related to the transfusion trigger (59,119). In the past, patients were generally transfused if the Hgb was below 10.0 g per dL, particularly during anesthesia (120). It is now generally recognized that most patients under general anesthesia tolerate an Hgb of 8.0 g per dL (121). Transfusion of RBC is now being delayed without difficulty in some cases until the Hct is 15% (58,63). This factor alone will influence transfusion requirements to an extent irrespective of any hemostatic effect of ANH.

There are many practical benefits to using ANH. The intraoperative collection of blood for ANH is simpler than is preoperative autologous donation and does not require any additional equipment or typing and cross-matching. ANH is easy to coordinate and requires minimal preoperative planning. Because the patient is in the operating room, the blood is readily available for immediate transfusion without delay. ANH is free of the risks of transfusion reactions and infection. ANH may slightly increase anesthesia and operative time; (73) however, obtaining the same amount of preoperatively donated blood is much more expensive and labor intensive (38,66).

In conclusion, ANH is a technique that can be used to reduce transfusion requirements associated with operations. Carefully controlled, prospective, randomized clinical trials are needed to further define the risks and benefits. Patient selection and optimal management, particularly in the patient with CAD, will need to be studied further. Hemodynamic response must be appropriately managed to reduce the incidence of myocardial ischemia in patients during ANH. The practice of ANH is variable, reflecting the many concerns and issues that still surround its use (38). The risk, benefit, and cost-effectiveness profile of ANH has yet to be determined. Future developments such as artificial oxygen carriers may reduce some negative effects of hemodilution and resulting reduced oxygen-carrying capacity. ANH is a safe therapeutic option to reduce the occurrence of blood transfusion associated with operations.

ANH is efficacious in certain clinical situations but is certainly not applicable to all patients and all surgical procedures. Astute clinicians must evaluate published trials, such as those reviewed in this chapter, and apply them to their own practice settings. Appropriate application of these and other perioperative interventions can benefit patients greatly by reducing blood loss, allogeneic transfusion requirements, transfusion-related expenses, and allogeneic transfusion-associated morbidity and mortality.

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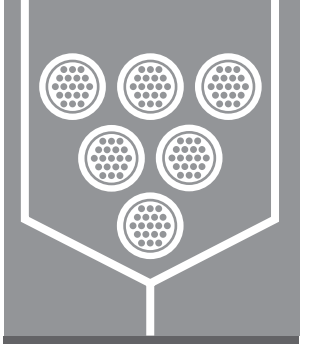

Hypothermia and Hemorrhage

35

Richard P. Dutton

Hypothermia—defined as a core temperature below 35°C—is a common finding in hemorrhaging patients. Emergency surgery, environmental exposure, and the need for rapid infusion of fluid and blood products contribute to the development of hypothermia. Hypothermia, in turn, disrupts the function of the coagulation cascade and contributes to coagulopathy. Hypothermia and coagulopathy comprise two thirds of the lethal triad that characterizes death from acute hemorrhagic shock (1). While hypothermia without hemorrhage is relatively benign—with a mortality of only 21% of patients with temperatures between 28°C to 32°C in one study (2)—hypothermia in hemorrhaging patients is almost universally fatal (3). Recognition of hypothermia is essential to achieving a good outcome in the hemorrhaging patient, as the past decade has seen the development of a number of devices and techniques which can arrest or even reverse the onset of hypothermia.

Because the chemical reactions of the body all have temperature-dependent rate constants, and because they must all work in synchrony, core body temperature is a closely regulated phenomenon. Conscious humans will become progressively uncomfortable as internal temperature drops and will change their behavior in response. This might include moving to a warmer location of a room or building, turning up the heat or decreasing the air conditioning, or covering up with more clothing or blankets (4). Conscious patients behave in the same way, but anesthetized patients lack this basic protective response, and must rely on other mechanisms to remain thermoneutral. Shivering to produce heat from muscular contraction occurs in both waking and sleeping humans, but is impaired in unconscious or deeply anesthetized patients. Redistribution of blood flow to conserve heat, driven by systemic reflexes, will occur in almost any patient. These mechanisms are limited in their capacity, however, and can easily be overwhelmed by perioperative events. If this occurs, body temperature will begin to drop, and the patient will become hypothermic. Hypothermia will continue until the patient is either externally warmed (by an attentive provider, for example) or awakens sufficiently to activate shivering reflexes and heat conservation behaviors.

CAUSES OF HYPOTHERMIA

Hypothermia is the result of loss of heat from the body in excess of metabolic production. Heat is lost to the environment by five principal mechanisms (5). *Radiation* is the transfer of heat from warmer objects to colder ones without direct contact. *Conduction* occurs from the skin to objects in contact with it, such as the operating room (OR) table, irrigating fluids, skin prep solutions, and the surrounding air. *Convection* is the facilitation of conductive heat loss by movement of the fluids involved (air currents, for example). *Evaporation* is the loss of heat to conversion of water from liquid to gaseous form, as occurs in the lungs and from exposed viscera. In addition, heat loss can occur by *dilution* of blood with colder liquids such as intravenous fluids or blood products. In all of these cases heat loss occurs more rapidly when the gradient of temperatures between the patient and the hypothermic agent is greater.

Hemorrhage contributes to hypothermia in a number of ways. Decreased perfusion of skin and muscle reduces heat loss to the environment, but also reduces metabolic heat production. Environmental exposure at the time of injury may be substantial, particularly if extrication from a

TABLE 35.1

CAUSES OF HEAT LOSS DURING HEMORRHAGE. EACH 60–75 KCAL OF ADDITIONAL HEAT LOSS RESULTS IN AN AVERAGE DECREASE IN CORE TEMPERATURE OF 1°C

Radiation:	Transfer of heat from warm objects to cooler ones without direct contact.
Conduction:	Transfer of heat from warm objects to cooler ones through direct contact.
■ External:	Spine board, OR table, skin prep solutions, irrigating fluids, surrounding air
■ Internal:	Crystalloids (16 kcal/L at 21°C), blood (30 kcal/L at 4°C)
Convection:	Transfer of heat to air or fluid moving across the body: drafts and irrigating solutions.
Evaporation:	Transfer of heat due to vaporization of liquid to gaseous water on the skin, respiratory mucosa, or exposed visceral surfaces.

(Adapted from Smith CE, Patel N. Prevention and treatment of hypothermia in trauma patients. In: Smith CE, Grande CM, eds. *Hypothermia in trauma—deliberate or accidental.* Baltimore, Md: International Trauma Anesthesia and Critical Care Society; 1997:11–16.)

damaged motor vehicle is required, or if the patient is wet from rain or firefighting spray. The average temperature of patients admitted following trauma is lower in cooler climates than in warmer (6). Environmental exposure continues in the emergency department (ED) as the patient is inspected for injuries and monitoring devices are placed. Evaporative loss is accelerated due to tachypnea, open wounds, and by any form of mechanical or assisted ventilation. In the OR, evaporative fluid and heat loss from open body cavities and exposed viscera may be substantial. Conductive loss is hastened by irrigation fluids used to wash out lacerations and open fractures. Table 35.1 summarizes mechanisms of heat loss in the hemorrhaging patient.

Fluid resuscitation itself is a major cause of hypothermia, as rapid infusion of room temperature crystalloids will directly reduce core body temperature. Administration of blood products taken directly from the refrigerator exacerbates this problem. A 70 kg patient undergoing resuscitation with 2 liters of crystalloid (at 21°C) and four units of red blood cells (at 4°C) over the first hour following admission will lose thermal energy equal to 152 kcal, leading to a temperature drop of 2°C absent rewarming efforts (5).

Effects of Hypothermia on Coagulation

Hypothermia by itself will produce a progressive deterioration in the rate at which clot forms. The rate constant of any biochemical reaction changes as temperature moves away from 37°C, and individual rates differ in their temperature sensitivity. As the patient becomes colder each individual reaction slows, the process as a whole becomes more desynchronized, and coagulopathy develops (7). Further, hypothermia leads to hepatic sequestration of platelets, (8) as well as morphological changes that lead to increased clumping and decreased functionality (9).

The dysfunction in coagulation related to hypothermia may be difficult to assay prior to the development of obvious nonsurgical bleeding. Routine coagulation tests (PT and PTT) sent from the ED and OR are performed on blood samples that are warmed to 37°C, as a means of standardizing the results. While a useful estimate of clotting factor *concentration,* these tests are not a reliable measure of in vivo clotting *function* (10). Table 35.2 shows the degradation in clotting factor function in normal human plasma that occurs at different temperatures. At 33°C, for example, the partial thromboplastin time will be prolonged to the same degree as it would be in a euthermic patient with a factor IX level of only 32%. A recent paper

TABLE 35.2

DEGRADATION OF CLOTTING FACTOR FUNCTION WITH HYPOTHERMIA. WHEN ASSAYED AT HYPOTHERMIC TEMPERATURES, PLASMA BEHAVES AS IF CLOTTING FACTOR DEFICIENT. AT TEMPERATURES LESS THAN 37°C, HYPOTHERMIA PROLONGS CLOTTING TO THE SAME EXTENT AS A REDUCTION IN FACTOR CONCENTRATION TO THE LEVEL SHOWN

>Temp	II	V	VII	VIII	IX	X	XI	XII
25°C	5	3	5	0	0	4	2	1
27°C	7	5	7	0	0	6	2	1
29°C	10	8	12	3	3	10	4	1
31°C	17	22	34	16	7	20	16	10
33°C	24	50	60	59	32	44	60	17
35°C	82	75	82	79	66	81	85	65
37°C	100	100	100	100	100	100	100	100

(Reprinted with permission from Johnston TD, Chen Y, Reed RL II. Functional equivalence of hypothermia to specific clotting factor deficiencies. *J Trauma.* 1197;37:413–417.)

examining the function of exogenous clotting factor VIIa under various conditions of temperature and acidosis arrived at similar conclusions (11).

Hypoperfusion resulting from hemorrhage may add to coagulopathy in other ways. Shock is not a static disease; pathophysiology may persist long after hemorrhage has been controlled and systemic resuscitation completed. The inflammatory process following injury is known to be a balance of many different cytokines, with the levels of individual factors determined by both the depth of shock sustained and the genetic makeup of the patient. Coagulation and inflammation are biochemically intertwined, and most procoagulant factors are also proinflammatory. The cascade of cellular signaling that occurs as ischemia develops may well include factors that directly decrease the rate of clotting or enhance fibrinolysis. Activated protein C is one such factor—the clinical use of this agent to modulate the inflammatory response in shock patients has been limited by its anticoagulant side effects (12).

Effects of Coagulopathy on Temperature Regulation

Death from acute hemorrhage is traditionally preceded by the lethal triad of hypothermia, coagulopathy, and acidosis. Acidosis is a function of decreased tissue perfusion, vasoconstriction, and the byproducts of anaerobic metabolism, and is usually the first leg of the triad to develop. Coagulopathy is due to consumption of factors, dilution with nonclotting fluids, and—as noted above—hypothermia. Hypothermia is both a cause and a result of coagulopathy, as failure of the coagulation system leads to increased bleeding, an increased need for resuscitative fluids, longer surgery, and further cooling (in the absence of meticulous fluid warming). Avoidance of coagulopathy thus becomes an important step in preventing hypothermia, just as avoidance of hypothermia is important in treating coagulopathy. The truth is that hypothermia and coagulopathy typically develop together, arising from the same underlying causes.

Modern warming technology makes it relatively easy to maintain a hemorrhaging patient at a temperature greater than 35°C, but this change has little impact on mortality from hemorrhage unless the other components of the triad are also addressed. Coagulation factors should be periodically measured and actively replaced, and sufficient fluid volume and anesthesia should be administered to maintain adequate tissue perfusion. Needless to say, nothing should interfere with surgical, angiographic, or medical interventions to control the source of hemorrhage, as any supportive therapies will be otherwise futile.

Therapeutic Potential of Hypothermia

Mild, moderate, and deep hypothermia have all been proposed and investigated as therapeutic options for the patient with either hemorrhagic shock or severe traumatic brain injury (TBI). Hypothermia reduces the metabolic rate, and thus the oxygen requirement, of the brain and heart. Deep hypothermia is a standard brain protective technique for surgeries requiring circulatory arrest (i.e., operations on the aortic root), while mild to moderate hypothermia is a routine component of cardiopulmonary bypass. There has long been interest in deliberate hypothermia in the bleeding patient, as a means of minimizing oxygen demand, reducing the degree of ischemia, slowing the release of inflammatory mediators, and thus improving long term outcomes.

Animal studies in models of uncontrolled hemorrhage have shown a survival benefit from the use of deliberate mild hypothermia (33°C to 35°C) (13,14). Improved neurologic outcomes have been demonstrated using mild to moderate hypothermia in animals with traumatic brain injuries (TBI) (15). Application of this therapy to human trauma patients has been controversial. Although a preliminary, single center trial of deliberate mild hypothermia to treat TBI patients showed improved outcomes, (16) a larger, multicenter trial did not confirm these results (17). Deliberate hypothermia in hemorrhagic shock patients has yet to be clinically studied.

Suspended animation or circulatory arrest with deep hypothermia (25°C) has been studied in a canine model of uncontrolled hemorrhage from an aortic injury (18). The concept consists of rapid cannulation of the central circulation, perfusion of the core vessels with a cold solution of protective chemicals (similar to the cocktails used to preserve transplanted organs), repair of the traumatic injuries during circulatory arrest, and then active rewarming via cardiopulmonary bypass. While good results have been achieved in dogs (full neurologic recovery), this technique will require the immediate availability of both expensive equipment and surgical expertise to be successful in patients. To date there has not been a successful human trial, although several have been proposed.

There are a number of variables that will limit the applicability of deliberate hypothermia as a therapeutic technique. The two most obvious are the impact on the coagulation system (discussed above) and the metabolic cost of rewarming. The beneficial anti-inflammatory properties of hypothermia are directly related to the harmful anticoagulant effects, in much the same way that procoagulant agents are also proinflammatory. Because effective control of hemorrhage is the sine qua non of resuscitation, it is unlikely that any therapy that worsens coagulopathy will be encouraged. Further, there is the potential for significant

metabolic stress during the process of rewarming and reperfusion, especially in older patients. Shivering and associated tachycardia can increase oxygen demand substantially, and may precipitate myocardial ischemia in susceptible patients (19).

In summary, while deliberate manipulation of core temperature has shown promise as a means of reducing secondary ischemic injury, this is still a laboratory phenomenon. The heterogeneity of hemorrhaging patients and the appropriate focus on rapid and complete control of bleeding make it unlikely that deliberate hypothermia will become a standard of care in the near future.

Treatment of Hypothermia

The best treatment for hypothermia during acute hemorrhage is prevention. Beginning with an awareness of the problem, health care providers must do everything possible to minimize heat loss from the bleeding patient. The ambient environment in the ED or OR should be increased (despite provider protestation) and periods of patient exposure should be minimized. Every effort should be made to keep the patient dry and covered against drafts. A humidifying filter or active warming device should be part of the ventilator circuit. Irrigation fluids used to lavage the thoracic or abdominal cavity should also be warmed to body temperature, especially as topical application of cold fluid to the surface of the heart may cause dysrhythmias and even cardiac arrest.

All fluids administered should be warmed to body temperature or slightly higher. A commercial fluid warmer is highly recommended for the ED or OR, and should be used whenever bolus fluid replacement therapy is underway. Blood products should be administered through an active warming system whenever possible. If blood is being given in an emergency it should be diluted with prewarmed isotonic crystalloid. This approach will both reduce the negative thermal burden of the blood and significantly increase the rate of flow through IV lines. For massive transfusions the use of a rapid infusion device is recommended, as this will allow for both warming to body temperature and powered infusion. Care must be taken to closely monitor the rate of flow through the rapid infusor, as excessive fluid administration is a dangerous possibility (20).

Rewarming is more challenging than maintaining thermoneutrality in the first place. A forced hot air blanket will achieve slow rewarming, if further heat loss is prevented and a sufficient area of the patient can be covered. Warming irrigation fluids, intravenous fluid, and inspired gases above normal body temperature will also result in positive heat transfer, but must be carefully managed to avoid burning the patient. For patients with severe hypothermia (core temperature below 30°C), and those who have already suffered a cardiac arrest, extracorporeal bypass (either veno–veno or arterio–veno) is the most effective method for restoring temperature. Methods for rewarming trauma patients are summarized in Table 35.3.

TABLE 35.3

METHODS FOR CONSERVATION OF HEAT AND REWARMING OF HYPOTHERMIC PATIENTS, IN APPROXIMATE ORDER OF TECHNOLOGICAL INTENSITY

Passive conservation of heat
- Increased room temperature
- Dry skin, clothes, and bedding
- Insulation with blankets

Active external warming
- Radiant lights (poorly effective in unconscious patients)
- Humidification with or without warming of inhaled gases
- Forced hot air blankets
- Warming of IV fluids

Active Internal warming
- Warmed irrigation fluids
- Continuous arterio-venous rewarming
- Hemodialysis
- Cardiopulmonary bypass

(Adapted from Smith CE, Patel N. Prevention and treatment of hypothermia in trauma patients. In: Smith CE, Grande CM, eds. *Hypothermia in trauma—deliberate or accidental.* Baltimore, Md: International Trauma Anesthesia and Critical Care Society; 1997:11–16.)

SUMMARY

Prevention and treatment of hypothermia is essential to the successful management of coagulopathy. Keeping the patient warm will not necessarily prevent hemorrhage, ischemia, or acidosis, but it will avoid the exacerbation of these conditions. Active and passive warming technologies should be available and should be used whenever possible. Attentive management can preserve core temperature in the face of even massive transfusion, and will have a beneficial effect on the prevention and treatment of coagulopathy.

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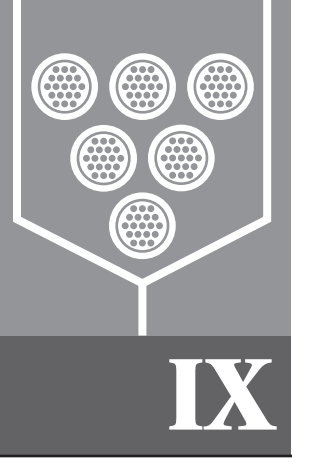
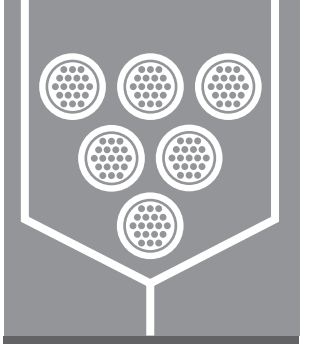


Transfusion and Surgical Subspecialties



36

Surgery In Patients with Red Cell Disorders: Sickle Hemoglobinopathies, Polycythemia, and Autoimmune Hemolytic Anemia

Imoigele P. Aisiku

The preoperative management of patients with sickle hemoglobinopathies or with polycythemia presents unique problems relating to transfusion medicine. Patients with sickle cell disease (SCD) are at risk for severe sickling (vaso-occlusive) complications in the postoperative period. The frequency of these complications can be reduced by preoperative transfusions because transfusions reduce the percent of circulating red cells capable of sickling. In the polycythemias, especially polycythemia vera, surgery is often complicated by episodes of thrombosis and/or hemorrhage due to increased blood viscosity and abnormal platelet function. For this reason, patients with uncontrolled polycythemia require preoperative phlebotomies to reduce blood viscosity by lowering the hematocrit. Anemias of most etiologies are corrected preoperatively with specific measures, such as iron for iron deficiency. Transfusions are used in anemic patients when specific treatment for their anemia is unavailable or when it is not likely to raise the hemoglobin level in time for surgery. Autoimmune hemolytic anemia is discussed as a special red cell disorder because it can present the difficult problem of identifying compatible units when transfusions are required. Preoperative management of the three red cell conditions discussed in this chapter requires close and continued collaboration between the surgeon and the hematologist, the anesthesiologist, and the transfusion medicine specialist.

SICKLE HEMOGLOBINPATHIES

Sickle Cell Disease

Sickle cell disease is a set of genetic abnormalities primarily affecting patients of African and Mediterranean descent. It is caused by a substitution of valine for glutamic acid in the sixth position of the beta globin chain (1–4). This alters

the surface charge of the molecule and allows sickle hemoglobin (Hb S) tetramers to polymerize inside the red blood cell (5,6). The polymer can alter both the red cell shape and membrane properties leading to abnormal interactions with the vascular endothelium (6,7). Sickle hemoglobin is a structural hemoglobin variant that aggregates or polymerizes when deoxygenated. There are several genetic variants of sickle cell disease. Generally, the most severe manifestations and disease course occur in Hb S patients (8). The most common and also the most severe form of sickle cell disease is sickle cell anemia (homozygous sickle cell disease, Hb SS) in which almost all intracellular hemoglobin is Hb S. Other forms of sickle cell disease are sickle cell-Hb C disease (Hb SC disease), in which Hb S and Hb C are present in equal amounts (each 50%), and the various types of sickle cell-β-thalassemias, which have 70% to 95% intracellular Hb S (9,10). Double heterozygotes for sickle trait and hemoglobin C or sickle trait and beta thallassemia also manifest clinically important forms of sickle cell disease, although a more benign disease course in general. The main hematological (11) and clinical characteristics of the various sickle cell genotypes are summarized in Table 36.1.

When Hb S is present in large enough amounts, it forms intracellular polymers at low but still physiological oxygen tensions (12). These polymers are rigid, liquid, crystallike structures that markedly decrease red cell deformity and ultimately result in membrane damage and erythrocyte sickling. The pathophysiological consequences of erythrocyte rigidity and sickling are twofold: a chronic hemolytic anemia due to premature destruction of the abnormal red cells and episodes of tissue injury, called vaso-occlusive, or painful, crises. The vaso-occlusive crises are thought to result from ischemia or necrosis due to impaired microvascular flow of the rheologically abnormal cells. There is evidence to suggest that the vaso-occlusive crisis of sickle cell disease represents a decompensated state in which a complex interplay of the inflammatory and the microcirculatory systems occur, resulting in abnormalities in microvascular function and oxygen transport. These changes lead inevitably to end-organ damage. The red cells of people with the sickle cell trait, the carrier state for the Hb S gene (Hb AS), have only 30% to 45% Hb S. This concentration is too low for Hb S polymerization to occur under normal physiological conditions. They are considered healthy and have no problems from their hemoglobin type except under special conditions (13).

Sickle cell patients frequently develop episodic multiple system complications. The accepted acute indications for transfusion include aplastic crisis, acute splenic sequestration, acute pulmonary sequestration associated with acute chest syndrome, and refractory priapism (14,15). Chronic transfusions are currently instituted for prevention of recurrent strokes. As discussed below, the most common complications are postoperative sickle cell chest syndrome and postoperative vaso-occlusive crisis.

Preoperative Risk Assessment

SCD patients have a high perioperative complication rate. Complications include pain crisis, ACS, erythrocyte alloimmunization, and transfusion reactions secondary to perioperative transfusion. Various reports have identified potentially predictive variables for postoperative complications (Table 36.2) (16). A history of pulmonary complications, pregnancy, URI, UTI, frequent hospitalizations, or an

TABLE 36.1
CHARACTERISTICS OF THE SICKLING DISORDERS

Genotype	Hb S (%)	Hb C (%)	Hb F (%)	Hb A (%)	Usual Hematocrit (%)	Clinical Severity
Sickle cell anemia (homozygous sickle cell disease, Hb SS)	80–95	0	1–15	0	20–30	++++
Sickle cell-hemoglobin C disease (Hb SC)	~50	~50	1–7	0	26–42	+to+++
Sickle cell-β^+-thalassemia (Hb Sβ^+ thal.)	70–90	0	2–10	10–30	30–42	+to++
Sickle cell-β^0-thalassemia (Hb Sβ^0 thal.)	70–95	0	2–20	0	20–35	++to++++
Sickle cell-δβ-thalassemia (Hb Sδβ thal.)	75–85	0	15–20	0	26–39	+to+++

TABLE 36.2
PREDICTORS OF POSTOPERATIVE COMPLICATIONS

Type of surgical procedure
Age beyond the second decade of life
Severity and frequency of SCD complications
Baseline abnormality on chest roentgenogram
Pregnancy
Concomitant infection

increase in the number of hospitalizations in the year before surgery were also identified in various reports to be independent predictors of perioperative complications (17–20). The assessment of SCD patients prior to surgery should therefore include a thorough history to identify disease severity and predictive factors as noted above.

The Cooperative Study of Sickle Cell Disease (CSSCD) followed prospectively 3,765 patients during the period from 1979 to 1988 (21). Koshy et al. (22) reported the surgery and anesthesia experience in 717 CSSCD patients (77% with Hb SS, 14% with Hb SC) who underwent 1,079 operative procedures. There were 12 deaths (1.1%) within 30 days after surgery, three (0.3%) of which were attributed directly to the surgery and/or anesthesia. No deaths occurred in patients younger than 14 years of age. Mortality rates of up to 3% were reported in earlier retrospective studies (23,24), whereas more recent series encountered little morbidity and no mortality (25–28). In all but one (28) recent series, preoperative transfusions were used routinely. Koshy et al. (22) also reported on the frequency of surgical procedures and their complications (Table 36.3).

Preoperative Transfusions

Prophylactic erythrocyte transfusion reduces the percentage of sickle hemoglobin, which theoretically reduces the complication related to increased RBC adhesion, sickling, polymerization, inflammation, hemolysis, and dehydration.

TABLE 36.3
COMMONLY PERFORMED PROCEDURES IN SCS (RATES OF COMPLICATIONS)

Cholecystectomy (7.8%)
Splenectomy (7.8%)
Dilation and curettage (18.6%)
Caesarean section & hysterectomy (16.9%)
Tonsillectomy and adenoidectomy (0%)
Myringotomy (3.9%)

Empirical Data supporting preoperative transfusions include:

1. Adding even small quantities of Hb A red cells to Hb SS red cells in vitro improves the rheological characteristics of the mixture (29).
2. The hyposthenuria and functional asplenia characteristic of children with sickle cell anemia can be reversed temporarily by transfusions (30,31).
3. Exchange transfusions improve exercise capacity in sickle cell patients without substantially raising their hematocrit, (32) suggesting that addition of Hb A red cells improves blood rheology and tissue perfusion also in vivo. This interpretation, however, has been challenged (33).
4. Vaso-occlusive complications such as pain crises, chest syndrome, and priapism are rare in children with sickle cell anemia who are on long-term transfusion programs.
5. A prospective randomized trial showed that prophylactic transfusions reduced the incidence of vaso-occlusive crises in pregnant patients with sickle cell anemia (34).

A lack of prospective data comparing transfusion with no transfusion arms results in recommendations from most hematologist supporting preoperative transfusions at least for patients with the more severe forms of sickle cell disease; sickle cell anemia and sickle cell β^0-thalassemia. In neurosurgical and cardiopulmonary bypass sickle cell disease patients, due to a lack of clear evidence for a conservative versus aggressive protocol, prophylactic transfusion is still recommended. Neurosurgical procedures (intracerebral aneurismal ablation) and cardiopulmonary bypass in sickle cell trait patients have recently been shown to tolerate bypass without specific transfusion protocols (35–37). In a recent review by Firth and Head, (16) they recommended a risk assessment profile to determine the need for transfusion. If hematocrit is approximately 30% transfusion may be beneficial in the moderate and high perioperative category and not indicated in the low perioperative category. If hemoglobin S is less than 30%, transfusion is potentially beneficial in the high risk category. Postoperatively, hypothermia, hypoxemia, hypovolemia, hyperviscosity, acidosis, and hypotension should be supportively managed. Appropriate fluid administration and analgesia should be provided. (38)

Simple Versus Exchange Transfusions

Simple transfusions are easy to perform and they lower the proportion of sickling cells in the recipient. This effect is more pronounced over time because the transfused red cells have a longer intravascular survival than the patient's own red cells and because simple transfusions raise the hematocrit, thus inhibiting endogenous erythropoiesis (39). Simple transfusions are the most practical option

when the patient's anemia is severe, as is the case with Hb SS disease. Conversely, because simple transfusions raise the hemoglobin level by approximately 1 g per dL per red cell unit (in adults), they are not appropriate for sickle cell patients with higher hematocrits, such as those with Hb SC disease or Hb S β^+-thalassemia (Table 36.1). In these patients, simple transfusions will raise the hematocrit to levels that could increase blood viscosity. Exchange transfusions are preferable because they rapidly lower the proportion of sickling cells without substantially raising the hematocrit. Other advantages of exchange transfusions for all sickle cell patients are:

1. A more physiological (lower) posttransfusion hematocrit;
2. A faster and more efficient reduction in the percent of sickling cells;
3. A much lower amount of iron loading per unit than with simple transfusions.

Disadvantages of exchange transfusions are a higher cost, exposure to more blood donors, and their need for adequate vascular access, which is a problem for many patients. Exchange transfusions can be accomplished by various manual methods (40) or with the use of automated equipment (erythrocytapheresis) (41). A simple method for manual exchange transfusion in sickle cell patients with an Hb level of at least 7 g per dL or a hematocrit of at least 20% is described below. For lower Hb or hematocrit values, 1 unit of RBCs (adults) or 5 mL per kg RBCs (children) can be administered before the exchange transfusion. Alternatively, if one unit (or 5 mL per kg) of RBCs is not expected to raise the Hb level to at least 7 g per dL, one can prepare the patient for surgery using simple transfusions instead of exchange transfusions.

The method for manual exchange transfusion is as follows:

1. Withdraw one unit of blood (450 mL) for adults or 7.5 mL per kg of blood for children from an arm vein.
2. Replace blood volume by rapidly infusing normal saline: 500 mL for adults or 8 mL per kg for children.
3. Repeat step 1.
4. Transfuse two units of packed RBCs for adults or 10 mL per kg packed RBCs for children.
5. Repeat steps 1 to 4 once more for patients with sickle cell anemia. Repeat steps 1 to 4 twice for patients with higher hematocrits (e.g., Hb SC disease).

With this method, four units of blood (adults) are removed and replaced with four units of packed RBCs plus 1,000 mL of normal saline. In adults with higher hematocrits, such as those with Hb SC disease, six units of blood are removed and replaced with six units of packed RBCs plus 1,500 mL of normal saline. After this manual exchange, the proportion of Hb A should exceed 50% and the proportion of Hb S (for sickle cell anemia) or of Hb S plus Hb C (for Hb SC disease) should be lower than 50%.

If automated equipment (blood cell processor, cell separator) is available, a red cell exchange, or erythrocytapheresis (42), can be performed. As with manual exchanges, four RBC units should be exchanged in adult patients with sickle cell anemia and six units in those with Hb SC disease. Automated red cell exchanges accomplish this objective while keeping the extracorporeal blood volume at about 250 mL (in adults). In contrast, the extracorporeal volume in manual exchanges can be up to 500 mL.

Aggressive Versus Conservative Transfusion Regimen

Vichinsky et al. (43) recently reported the results of a prospective, multicenter, randomized clinical trial comparing two approaches to preoperative transfusions in sickle cell anemia. Over 600 surgical procedures in 551 Hb SS patients were randomized preoperatively to an *aggressive* or *conservative* transfusion regimen. The aim of the aggressive regimen was to achieve a preoperative Hb level of at least 10 g per dL and an Hb S fraction of 30% or less. This regimen usually required exchange transfusions. The objective of the conservative regimen was to maintain an Hb level of 10 g per dL (range 10 to 11) regardless of the percent Hb S. Most patients in this regimen received simple transfusions. A *no-transfusion* randomization arm was not included because most investigators agreed that some form of preoperative transfusions were necessary in patients with sickle cell anemia undergoing surgery. Both children and adults participated in the trial, and elective and emergency surgical interventions were performed. The anesthesia risk score was three in 51% of the patients and two in 47% of the patients. The most common operations were cholecystectomy, ENT (ear, nose, and throat), and orthopedic procedures. Over 80% of the procedures were carried out using a combination of inhalation and intravenous anesthesia, and the average duration of the anesthesia was 2.5 hours. Table 36.4 shows that the aggressive regimen was no better than the conservative regimen in preventing postoperative sickling complications, the most common of which was sickle cell chest syndrome (10% of the cases in both treatment arms). The frequencies of postoperative fever or infection and pain crises ranged from 4% to 7% and were not affected by the preoperative transfusion regimen. In contrast, the frequency of transfusion complications was much higher in the aggressive transfusion arm, presumably because of exposure to a larger number of RBC units. The appearance of new RBC alloantibodies was twice as likely in the aggressive transfusion arm (10% versus 5% in the conservative regimen; $P = .01$). Hemolytic transfusion reactions occurred in 6% of cases managed with aggressive transfusions. Only 1% of patients in the conservative transfusion

TABLE 36.4
CLINICAL TRIAL OF CONSERVATIVE VERSUS AGGRESSIVE PREOPERATIVE TRANSFUSION REGIMEN IN SICKLE CELL ANEMIA

	Conservative (77% with Simple Transfusions)	Aggressive (57% with Exchange Transfusions)
Patients/operations	273/301	278/303
Mean pretransfusion Hb (g/dL)	7.9	8.0
Mean number RBC units transfused		
Children (birth to 9 yr)	1.5	3.8
Adults	3.3	6.1
Mean posttransfusion Hb (g/dL)	10.6	11
Mean posttransfusion Hb S (%)	59	31
Postoperative complications		
Chest syndrome (%)	10	10
Fever or infection (%)	5	7
Pain crisis (%)	7	4
Transfusion complications		
Hemolytic transfer reaction (%)	1	6
New RBC alloantibody (%)	5	10

Adapted from Vichinsky EP, Halurkern CM, Neumayr L, et al. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. *N Engl J Med.* 1995;333:206–213.

arm developed this problem. Multivariate analysis showed that a higher surgical risk category and a history of pulmonary disease were independent risk factors for the most severe postoperative complication, the sickle cell chest syndrome. Age greater than 10 years and over five previous hospitalizations were associated with the development of postoperative pain crisis. This controlled study (43) indicates that, contrary to expectation, exchange transfusions, or other intensive transfusion regimens that lower the Hb S fraction to less than 50%, are no better than simple transfusions in preventing postoperative vaso-occlusive events. Therefore, simple transfusions are at present preferable in the preoperative preparation of sickle cell anemia patients. Limited exchange transfusions might still be required preoperatively for those few SS patients with higher hematocrits. Furthermore, once a perioperative vaso-occlusive complication has developed, therapeutic exchange transfusions are indicated.

Preoperative Transfusions in Hb SC Disease and Other Less Severe Genotypes

The clinical course of Hb SC disease is variable (44,45). In general, however, patients with this or with other genotypes that have less hemolysis and less anemia also tend to have a lower vaso-occlusive severity. In the report from the CSSCD (22), 102 Hb SC patients had surgical procedures, and preoperative transfusions were associated with lower rates of postoperative crises and chest syndrome. At our center, we recommend preoperative exchange transfusions in Hb SC disease and sickle cell R+-thalassemia when at least one of the following conditions is present:

1. Ophthalmological procedures, usually vitrectomy, with risk of anterior segment ischemia and/or secondary glaucoma (46);
2. High-risk procedures such as cardiopulmonary bypass (47);
3. Surgery in which substantial blood loss is expected, such as total hip arthroplasty (48); in these cases, perioperative transfusions are likely to occur anyway;
4. Patients with particularly severe clinical course, such as those with three or more hospitalizations for vaso-occlusive crises and/or chest syndrome per year;
5. Presence of risk factors that have been shown to predict postoperative chest syndrome in Hb SS disease in the controlled study discussed above (43).

Recommendations

Because sickle cell disease has a wide spectrum of severity, preoperative transfusion management has to be individualized. Hemoglobin electrophoresis should always be obtained preoperatively in patients with a previously undiagnosed anemia and clinical risk factors for sickle cell anemia. If the patient has sickle cell disease (Table 36.1), hematological consultation should be sought for joint

perioperative management, (49) particularly for decisions involving transfusion. Transfusions are indicated for all surgical interventions requiring general anesthesia, even those that are not particularly invasive such as laparoscopic surgery and debridement or skin grafting of leg ulcers. Although there is limited evidence, regional anesthesia patients should undergo similar preoperative transfusion guidelines as general anesthesia. The CSSCD series reported more complications in patients operated under regional anesthesia. The estimated odds ratio was 2.32 when compared with general anesthesia (22). This was not a primary endpoint of the study and was susceptible to selection bias and therefore only conjectures can be made. Table 36.5 summarizes the preoperative transfusion recommendations for the various forms of sickle cell disease. These recommendations are based on the best currently available information but are not meant to substitute for informed clinical judgment in the individual patient.

Avoidance of Transfusion Reactions

The prevalence of RBC alloimmunization in sickle cell disease is about 20%, (50) and these patients have a high risk for delayed transfusion reactions (51). Obtaining an alloimmunization history before any transfusions are given is essential to avoid these reactions. A detailed history on transfusion history, transfusion reactions, and known alloantibodies should be obtained to minimize transfusion reactions. If the patient has a history of having formed a red cell alloantibody, RBC units that are negative for the corresponding antigen should be requested even if the current antibody screen no longer shows that antibody. This is a result of up to 50% of the RBC alloantibodies formed by sickle cell patients (50) and by other patients (52) become serologically undetectable within a year. These patients when transfused with RBCs bearing the antigen(s) responsible for the primary immunization, a strong anamnestic antibody response occurs and a life-threatening delayed hemolytic transfusion reaction can develop. In preoperatively transfused patients, these reactions typically take place during the postoperative period.

TABLE 36.5
RECOMMENDATIONS FOR PREOPERATIVE TRANSFUSIONS IN THE SICKLING DISORDERS

Sickle cell anemia, sickle cell- β^0-thalassemia, or sickle cell-$\delta\beta$ thalassemia (Hb SS, Hb S-β^0 thal., or Hb S-$\delta\beta$ thal.)
Hematocrit 20%–30%[a]
Simple transfusion 3 units RBCs (adults)
Simple transfusion 15 mL/kg RBCs (children)
Hematocrit >30%
Exchange transfusion 4–6 units RBCs (adults)
Exchange transfusion 15 mL/kg RBCs (children)
Sickle cell-hemoglobin C disease or sickle cell- β+-thalassemia (Hb SC or Hb Sβ+ thal.)
Hematocrit <25%
Simple transfusion 3 units RBCs (adults)
Simple transfusion 15 mL/kg RBCs (children)
Hematocrit >25%
Individual consideration (see text)
If transfusions needed use
Exchange transfusion 4–6 units RBCs (adults)
Exchange transfusion 15 mL/kg RBCs (children)

[a]For lower pretransfusion hematocrits, additional units should be used.

Types of RBCs Units to be Used

Sickle-negative RBC units should be used because interpretation of posttransfusion Hb S levels can be problematic in patients transfused with RBCs from sickle cell trait donors. Patients should be given leukodepleted RBC units to avoid febrile transfusion reactions or to avoid primary immunization to leukocyte antigens.

Because of the high risk of alloimmunization (see above), the use of extended RBC antigen matching for all sickle cell patients, regardless of transfusion history, has been recommended (43,53,54). The arguments in favor of this recommendation are that transfusion history may be unreliable or unavailable and that screening donors for most antigens against which sickle cell patients form antibodies is relatively simple. Prospective randomized studies to assess the risk-to-benefit ratio of this approach to solve the alloimmunization problem have not been conducted (55). One can predict that matching for the common RBC antigens will still fail to prevent alloimmunization in as many as 25% of sickle cell patients (56). Furthermore, requesting antigen-matched RBCs for preoperative transfusions in non-alloimmunized sickle cell patients could lead to unnecessary delays in the surgical procedure. For these reasons, antigen-matched RBCs for preoperative transfusion of non-alloimmunized patients are justified only if such a request does not delay transfusion and/or surgery.

Sickle Cell Trait

People with the sickle cell trait (Hb AS) do not have sickle cell disease. They have no hemolysis or anemia because the fraction of Hb S in their red cells is too low for polymerization to occur in vivo. An excellent review of the few medical risks thought to be associated with sickle cell trait was published recently (57). Increased surgical risk has not been demonstrated (58,59), and preoperative transfusions in sickle cell trait are not needed unless the patient is anemic from an unrelated illness. Based on rare adverse events (60–62), some recommend exchange transfusions for procedures where hypoxia or hypoperfusion may occur,

including open heart and intrathoracic surgery (63,49). Reports from other investigators, however, do not support the need for this recommendation (64).

Autologous Transfusions

An increasing number of preoperatively deposited autologous units are being transfused to surgical patients without sickle cell disease (566,000 units in the United States in 1992 (65)). As stated earlier, however, the objective of transfusions in sickle cell patients is to lower the proportion of red cells capable of sickling to prevent postoperative complications. Replacement of intraoperative blood losses by previously collected autologous RBCs would increase the percent circulating SS RBCs and work against the protective effect of the preoperatively transfused isologous (Hb AA) RBCs. Therefore, autologous units should not be used. There is a report of a fatality, presumably from widespread sickle cell sequestration and disseminated intravascular coagulation, after intraoperative transfusion of autologous Hb SC RBCs (66).

Transfusion of intraoperatively salvaged RBCs is possible but is likely to be safe only in sickle cell patients who have undergone preoperative isologous exchange transfusions. Under these circumstances, the salvaged RBCs are mostly isologous (Hb AA type) and only a small proportion of them (less than 50%) are really autologous (Hb SS). The safety of transfusing autologous RBCs salvaged during surgery in patients who have not received preoperative isologous RBCs has not been shown. The salvage procedure also could pose technical difficulties. Sickle RBCs that are not *diluted* by isologous (Hb AA) RBCs have a tendency to clump in centrifugation bowls (67) and may do the same in the cell saver. Limited evidence (68) has suggested the possible use of RBCs salvaged during surgery only if the proportion of SS cells has been lowered to less than 50% via preoperative isologous (Hb AA) transfusions. Generalizations cannot be made due to the lack of strong literature based evidence.

The situation is quite different in sickle cell trait. Surgical patients with Hb AS should take advantage of alternatives to isologous transfusions (69) just like patients without sickle hemoglobin. There are no studies of autologous transfusions in people with sickle cell trait. There are a half million autologous units transfused yearly in the United States (62) and no known adverse reports in patients with sickle cell trait have been reported. Liquid storage of Hb AS red cells does not appear to affect their intravascular survival in autologous (70) or homologous (71,72) recipients. Frozen storage of Hb AS red cells, however, requires special procedures during the deglycerolization process to avoid hemolysis (73,74). Also, there may be problems when using filters for leukodepletion of sickle trait units after their liquid storage (75). It should be possible to use the cell saver for intraoperative autotransfusion in sickle cell trait. However, there is a report of sickling of Hb AS RBCs after their collection in the cell saver so that autotransfusion was not carried out and its safety was questioned (76).

Hydroxyurea and Other New Therapies

Fetal hemoglobin (Hb F) inhibits Hb S polymerization and sickling of Hb SS erythrocytes (77). The antineoplastic agent hydroxyurea increases Hb F and thus improves the anemia in homozygous sickle cell disease (78). The mechanism is currently poorly understood. In a recently published clinical trial, Charache et al. (79) showed that this drug also reduced the frequency of painful crises, chest syndrome, and transfusions in sickle cell anemia. Participants in this trial were adult SS patients who had at least three crises per year so that they had moderate to severe sickle cell disease (56% of them had over six crises in the year preceding the study). The effect of hydroxyurea on surgery, the postoperative sickle cell complications, and the indications for preoperative transfusions is currently not known. Further studies are required to delineate the role of hydroxyurea therapy on surgical guidelines. Bone marrow transplantation has been utilized with increasing frequency. Patient selection, procedural complications, donor compatibility, and varying cure rates have limited widespread use. Various reports have reported success rates in the US of 70% to 80% and as high as 90% to 95% in 5-year survival and cure rates in some European literature (80–82). Other drugs that can increase fetal hemoglobin in sickle cell anemia are under investigation (83). Other potential experimental therapies include antidehydration agents (Clotrimizole derivative ICA-17043, Dipyridamole, and N-acetylcysteine) (84–86). If proven clinically effective, their use could dramatically reduce the need for all transfusions, including preoperative transfusions. The treatment of sickle cell disease is evolving with a renewed interest in the chronic management of sickle cell disease. Improved therapies to manage and prevent the complications may impact the morbidity and mortality around surgical procedures in these patients.

POLYCYTHEMIA

Polycythemia or erythrocytosis denotes an elevated hemoglobin concentration and packed red cell volume (hematocrit). The increased hemoglobin concentration can be due to absolute erythrocytosis, in which there is an elevated red cell mass, or to relative erythrocytosis (spurious erythrocytosis, spurious polycythemia), in which there is

reduced plasma volume. Only absolute erythrocytoses are discussed in this chapter.

Classification

The polycythemias can be classified pathophysiologically into two categories.

Polycythemias Caused by Increased Erythropoietin (Secondary Polycythemias)

A variety of clinical conditions leading to blood or tissue hypoxia (e.g., residence at high altitude, pulmonary diseases, cyanotic congenital heart diseases, high oxygen affinity hemoglobins, and carbon monoxide intoxication) are associated with erythrocytosis (87). Neonates have high red cell volume in response to intrauterine hypoxia and the high oxygen affinity of fetal hemoglobin. The increased erythropoietin secretion responsible for these polycythemias is appropriate because it represents a physiological response to hypoxia. Other secondary polycythemias are due to inappropriate release of erythropoietin or erythropoietinlike substances from abnormal, predominantly neoplastic tissues. Examples include polycythemias due to renal cysts and tumors, hepatomas, and cerebellar hemangiomas.

Polycythemias Without Increased Erythropoietin (Primary Polycythemias)

Polycythemia vera (P. vera) is by far the most common and important type of primary polycythemia. This condition and its preoperative management are discussed below. Other forms of primary polycythemia are rare. Familial forms could be due to increased sensitivity of erythroid progenitor cells to erythropoietin.

Definition and Incidence

P. vera is a neoplastic clonal stem cell disorder characterized by excessive marrow hemopoiesis in the presence of low erythropoietin levels (88). The annual incidence of P. vera in the United States is approximately five to 17 cases per million (89,90). The average age at diagnosis is 60 years, and the disease is extremely rare before 30 years of age.

Clinical Features and Course of the Disease

Most patients with P. vera have a prolonged survival (91). Patients may present without any symptoms, and on routine examination they may have erythrocytosis, thrombocytosis, or splenomegaly. However, the clinical picture in untreated patients then evolves into a long symptomatic phase due to excessive production of blood cells of various lineages. Symptoms are frequently nonspecific and may be related to impaired cerebral blood flow from increased blood viscosity. Headache, weakness, weight loss, pruritus, visual disturbances, paresthesias, excessive sweating, and joint pain are frequent complaints. Venous and arterial thromboses are the most common serious complications. The physical findings in P. vera include ruddy cyanosis, conjunctival plethora, hepatomegaly, splenomegaly, and hypertension (88,92). The proliferative phase of P. vera is frequently followed by a stage, postpolycythemic myeloid metaplasia (93), in which the patient no longer suffers from the consequences of erythrocytosis but is now anemic or pancytopenic, has gross splenomegaly, and is cachectic. This phase (spent polycythemia) resembles the terminal stage of a malignant tumor (94). In fact, a number of P. vera patients will ultimately go on to develop acute myeloid leukemia (95).

Diagnosis

The criteria for diagnosis of P. vera have been defined by the Polycythemia Vera Study Group (96). The diagnostic criteria have been classified into two categories based on their relative significance:

1. Category A
   - A1. Increased red cell volume (measured with ^{51}Cr-labeled red cells): men at least 36 mL per kg and women at least 32 mL per kg;
   - A2. Normal arterial oxygen saturation (at least 92%);
   - A3. Splenomegaly.
2. Category B
   - B1. Thrombocytosis: platelets at least 400×10^9 per L;
   - B2. Leukocytosis: white cells at least 12×10^9 per L;
   - B3. Elevated leukocyte alkaline phosphatase score (greater than 100) in absence of fever or infection;
   - B4. Elevated serum vitamin B_{12} level or B_{12} binding capacity: B_{12} more than 900 pg per ml; $UB_{12}BC$ (binding capacity) more than 2,200 pg per mL.

The diagnosis of P. vera can be made if all three criteria in category A are present or the combination of an elevated red cell volume and a normal oxygen saturation is present with any two parameters from category B.

Thrombotic and Hemorrhagic Complications

Untreated patients with polycythemia are at a high risk of both thrombosis and hemorrhage. Thrombosis was listed as a cause of death in as many as 37% of fatalities in P. vera (91,97). Patients may develop deep venous thrombosis of the lower extremities and cerebral, coronary, or peripheral artery occlusion (98). Erythromelalgia with burning pain in the digits is a common symptom. Painful ulcerating lesions of the toes and fingers may develop. Other vascular events include Budd-Chiari syndrome; pulmonary embolism; and thrombosis of mesenteric, hepatic, or

splenic arteries (99). Transient ischemic episodes, cerebral infarction or hemorrhage, dementia, choreic syndromes, and paresthesias occur in a large percentage of untreated patients with P. vera (100). Bleeding complications are a cause of death in 5% to 10% of P. vera patients and as many as 30% to 40% of patients may experience serious hemorrhagic events (101). Epistaxis, gingival hemorrhages, gastrointestinal bleeding, or hematomas involving vital organs may develop. Patients with uncontrolled P. vera have a high risk (79%) of complications during and after surgery (101–104). Thrombosis, hemorrhage, or both may develop.

Treatment of P. Vera and Secondary Polycythemias

Phlebotomy is the initial treatment recommended for P. vera. Patients who are less than 40 years of age should be managed with phlebotomies alone (105). If phlebotomies cannot control the increased hematocrit or if thrombocytosis with its associated thrombosis risk is present, myelosuppression with hydroxyurea is indicated. Radioactive phosphorus is used to achieve myelosuppression in patients over 70 years of age. It is not used in younger subjects because of its leukemogenesis risk. The immunomodulatory agent interferon α-2b, anagrelide (a selective inhibitor of platelet production), and antiplatelet medications have all been used to treat P. vera. The choice of therapy remains a subject of active debate. Therapy should be individualized, and a combination of different approaches is often necessary (106,107). The goal of therapy is to maintain the hematocrit at 42% to 45% and to prevent thrombotic complications.

The main therapeutic goal in secondary polycythemia is to correct, if possible, the condition responsible for the increased erythropoietin production. Phlebotomies are used to lower the hematocrit and prevent hyperviscosity while the primary condition is being corrected or when it is untreatable. Some have reported successful management of the polycythemia of cyanotic congenital heart disease using hydroxyurea instead of phlebotomies (108). Neonates who are small for gestational age and those born to diabetic mothers can have hyperviscosity due to an excessively high hematocrit (more than 65%) and may require treatment with exchange transfusion.

Recommendations for Preoperative Management

In patients with uncontrolled P. vera, surgical procedures are associated with development of serious complications due to hemorrhage, thrombosis, or both. As many as 75% of patients may develop these complications and approximately one third could die as a result (102–104). The frequency of these complications can be reduced to 28% by preoperative measures that normalize the hematological parameters. Treatment should be individualized. The following recommendations are offered as a general guideline for preoperative management of patients with P. vera:

1. Elective surgery and dental procedures should be postponed until the red cell mass and the platelet count have been normalized for at least 2 months. The longer the hematological control has been in effect, the lower the frequency of complications in the postoperative period.
2. In case the patient requires an emergency procedure, intensive phlebotomy treatment accompanied by replacement with plasma should be carried out. The rate of blood removal will depend on the patient's hemodynamic status. The goal is to reduce the hematocrit to around 42% to 45%. The platelet count may be reduced using plateletpheresis. The value of antiplatelet agents such as aspirin in preventing thrombosis is questionable.

Therapeutic venesection to improve cerebral blood flow and increase exercise tolerance may also be indicated in patients with secondary polycythemias such as those due to pulmonary disease and cyanotic congenital heart disease (109,110). In these secondary polycythemias, the hematocrit should be maintained at about 50% and 55% to 60%, respectively. In neonates, partial exchange transfusion may be needed to decrease the hematocrit to acceptable levels (55% to 60%).

AUTOIMMUNE HEMOLYTIC ANEMIA

Autoimmune hemolytic anemias (AIHA) (111) are characterized by the presence of an autoantibody directed against antigens on the red cell membrane and by shortened red cell life span occurring as a result of this antibody. The autoantibodies are of three general types: cold agglutinins, virtually always IgM, which cause clumping of red cells at cold temperatures; warm antibodies of IgG type, which bind to red cells at 37°C but do not agglutinate them; and Donath-Landsteiner antibodies, rare antibodies of IgG isotype, which fix to the red cell membrane at cold temperatures and activate the hemolytic complement pathway when the cells are warmed to 37°C. AIHA can be due to an underlying disease (secondary AIHA) or can develop without such diseases (idiopathic AIHA).

AIHA has an annual incidence of approximately 1 in 80,000. It affects all age and ethnic groups but is more common in midlife and in women. Most cases of AIHA are due to warm antibodies (70% to 80%). Cold agglutinin disease (CAD) is less common (10% to 20%) and paroxysmal cold hemoglobinuria (PCH) due to a Donath-Landsteiner antibody accounts for a small percentage of all patients with AIHA (2% to 5%). Approximately half the cases are

secondary to an underlying disease, most commonly a lymphoproliferative disorder. Other cases are induced by drugs, and in some patients, AIHA is a component of an autoimmune disease such as systemic lupus erythematosus.

Clinical Findings

The disease can present acutely or may be discovered incidentally by a positive antiglobulin (Coombs') test when a patient is referred for transfusion therapy. Clinical features include jaundice, symptoms and signs of anemia, and splenomegaly. Jaundice is usually mild, and splenomegaly is present in approximately one third of the patients. The presence of lymphadenopathy, petechiae, fever, hypertension, or renal failure should point to the possibility of an underlying disease in a patient with AIHA. Intravascular hemolysis with accompanying hemoglobinuria and hemosiderinuria occurs in both CAD and PCH.

Diagnosis

A positive direct Coombs' test (antiglobulin test) in the presence of hemolysis is the hallmark of AIHA. The direct Coombs' test detects autoantibodies on the red cells. These antibodies destroy red cells either by intravascular complement-mediated hemolysis or, more frequently, by opsonization and reticuloendothelial system phagocytosis. A positive indirect Coombs' test is due to the presence of antibodies in the serum. In 80% of patients with the warm antibody type of AIHA, both direct and indirect Coombs' tests are positive. A positive indirect Coombs' with a negative direct Coombs' test usually indicates the presence of alloantibodies induced by prior transfusions or pregnancies. Alloantibodies bind only to red cell antigens not present on the patient's red cells.

A Coombs' test is frequently positive during the acute attacks of PCH, and a Coombs' test done with anti-C3 or anti-C3dg is often positive in CAD (112). Cold antibodies are generally present in high titers but are not detected by the antiglobulin test because the IgM antibodies easily dissociate from the erythrocytes during the washing procedures and at warmer temperatures. The Coombs' test can be falsely positive in 8% of patients and may be falsely negative in 2% to 4% of all cases of AIHA. More sensitive tests such as the antiglobulin consumption test or tests with ^{125}I-staphylococcal protein A may be needed (113,114). Patients with AIHA can have both autoantibodies and alloantibodies (from recent or remote transfusions), causing difficulties in identifying the antibody responsible for hemolysis. Specialized reference laboratories may be required for accurate diagnosis in such cases.

Treatment of AIHA

When an underlying disease is responsible for the production of the autoantibody, treatment is directed to the management of the primary problem. The prognosis is dependent on the primary disease and its response to therapy. In patients with postinfectious PCH and CAD, hemolysis is generally self-limited. In those with idiopathic forms of CAD, the disease is generally mild, and avoidance of cold is often sufficient to prevent severe anemia. Plasmapheresis, cytotoxic chemotherapy, or interferon may be used in patients with CAD who have severe anemia. In idiopathic PCH, red cell destruction can be marked and transfusions may be required (see below).

Steroids are the preferred initial treatment for AIHA of the warm antibody type. Patients with severe disease may require transfusions. Most children with AIHA will achieve a complete remission with steroids. However, permanent remissions are unusual in adults. Splenectomy is indicated in patients who do not respond to steroids or who relapse during or after decreases in the dosage of prednisone (115). If possible, patients should be immunized with pneumococcal vaccine several weeks before splenectomy. Patients who do not respond to splenectomy may benefit from immunosuppressive therapy, danazol, or high-dose intravenous immune globulin. Occasional dramatic responses have been reported with plasma exchange in patients who were being prepared for surgery (116).

Transfusions in Patients with AIHA

In AIHA, transfusions are reserved for those patients with severe symptomatic anemia. Severe anemia may cause high-output cardiac failure, pulmonary edema, tachycardia, light headedness, chest pain, and restlessness or somnolence. Patients with these problems need to be transfused, but transfusions pose special problems in AIHA (117–121). The patients may have to be transfused with in vitro *incompatible* or *least incompatible* red cell units. Also, as mentioned above, alloantibodies may be present because of previous transfusions or maternal-fetal incompatibility (122,123). These alloantibodies can be difficult to identify in the presence of AIHA so that an alloimmunization history is crucial (see Avoidance of Transfusion Reactions, Sickle Cell Disease, above). Oxygen (100%) may be beneficial because the plasma is capable of carrying a small amount (0.3 mL per dL) of oxygen, but it is no substitute for red cells. The clinician must work closely with the blood bank in making the decision to transfuse these patients. Table 36.6 lists general guidelines for transfusing patients with AIHA.

TABLE 36.6
GENERAL GUIDELINES FOR TRANSFUSING PATIENTS WITH AUTOIMMUNE HEMOLYTIC ANEMIA

1. If cardiac or cerebral function is threatened, transfuse without delay even before all the serological testing is complete.
2. In patients without a history of previous transfusions or pregnancy, ABO and Rh-compatible red cells are generally safe to administer.[a]
3. In patients who have been pregnant or transfused previously, testing for alloantibodies is essential. Give red cells as described in item 2 above. These units should be negative for the antigen(s) against which the alloantibody(ies) is directed.
4. Transfuse relatively small amounts of red cells (0.5–1 unit of packed RBCs in adults and 2–5 mL/kg in children). These quantities are often sufficient to alleviate signs and symptoms of anemia. Overtransfusion can precipitate or worsen cardiac failure.
5. Patients with CAD and PCH should receive prewarmed and preferably washed red cells.
6. Blood should be administered slowly and leukocyte filters should be used to prevent reactions, which may be confused with hemolytic reactions.
7. Administer furosemide after transfusion and observe the patient closely for 6–12 hours for signs and symptoms of fluid overload.
8. Monitor patients for hemolytic transfusion reactions. Acute intravascular hemolysis can occur in the absence of any serological incompatibility.
9. In preparation for surgery, transfuse to increase the hemoglobin concentration to approximately 8 g/dL.

Adapted with permission from Jefferies LC. Transfusion therapy in autoimmune hemolytic anemia. *Hematol Oncol Clin North Am.* 1994;8:1087–1104.
[a]Sometimes autoantibodies react less strongly in vitro with cells lacking specific antigens (e.g., Rh antigens in warm type AIHA and I or M antigens in CAD). In such cases, RBC units that are negative for these antigens may be selected, if available.

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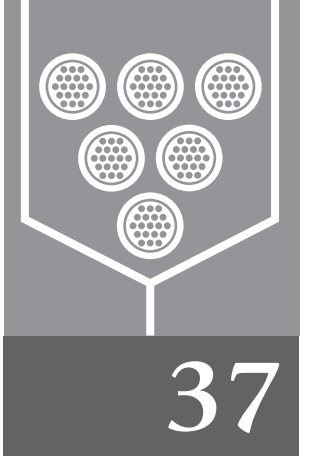

Surgery in the Jehovah's Witness

37

Richard K. Spence Aryeh Shander Zenon Bodnaruk Michael Huber

From time to time, surgeons may have as a patient a member of the Jehovah's Witnesses faith. This can be a positive or a negative experience, depending on how much the surgeon understands about the beliefs of the Jehovah's Witness and the constraints they may place on medical care. Individual physician responses vary; some refuse to treat Jehovah's Witness patients; some seek out non-Witness family members to override the patient's decision; and some seek legal protection through court orders permitting transfusion. A common response in the past was to take a presumed higher moral ground based on the physician's beliefs and to proceed with transfusion despite the patient's wishes. Still other physicians have suffered from what has been called the *paralysis of anemia*, or failure to stop bleeding, e.g., performing a splenectomy for a ruptured spleen, because of fear that the patient would die without transfusion. Unfortunately, this course has led to clearly avoidable patient deaths. In our experience, many physicians have either little understanding or an incorrect understanding of the Witnesses' position. They consider the Jehovah's Witnesses to be either medical nihilists or kooks. If the surgeon is to make intelligent informed choices in dealing with Jehovah's Witnesses patients, it is important that he or she have a clear understanding of their positions on medical care, specifically transfusion.

The Jehovah's Witnesses religion started in the early 1800s, growing out of a bible study group that believed in the imminent second coming of Christ and His rule over the earth for the ensuing 1,000 years. The group was further organized and led by Charles Taze Russell in the 1870s. Russell expanded the role of Bible study and promoted the group's beliefs through the publication of religious tracts and books. In 1884, the group became known as the Zion's Watch Tower Tract Society. Joseph Franklin Russell assumed leadership of the religious group in 1916 upon Charles Russell's death. He used his talents as an attorney and organizer to restructure the group into a centrally run religion that became known in 1931 as the Jehovah's Witnesses. Under his tutelage, the Jehovah's Witnesses further developed their goals of Bible study and community missionary work. A governing body based in Brooklyn Heights, New York, currently runs the religion (1).

Of primary concern to surgeons is the Jehovah's Witnesses' refusal to accept blood transfusion. This belief is based on a strict interpretation of passages from the Bible:

> Every moving thing that liveth shall be meat for you; even as the green herb have I given you all things. But the flesh of the life thereof, ye shall not eat. (Genesis 9:3–4)
>
> For it (blood) is the life of all flesh; the blood of it is for the life thereof: therefore I say unto the children of Israel, ye shall eat the blood of no manner of flesh: for the life of all flesh is the blood thereof. Whosoever eateth it shall be cut off. (Leviticus 17:14) (KJV)

One can argue interminably that these passages should not be interpreted to include blood transfusion or that such dietary prohibitions have no place in the modern world. However, the true Jehovah's Witness cannot be dissuaded and frequently counters any philosophical or religious arguments with sound scientific reasons why blood transfusion is inherently dangerous (2).

Physicians must realize the importance of the refusal to accept transfusion for the Jehovah's Witness. This is not a minor infraction, punishable by a slap on the wrist. The consequences of transfusion for the Jehovah's Witness include excommunication from the church, forfeiture of a chance for eternal life, and severance of the individual's

relationship with God. Although it may be difficult for a physician to accept this position, especially in a situation where transfusion can be lifesaving, one must understand that the potential for life everlasting is an enormous incentive, especially when the alternative is so negative. Each surgeon must make a personal decision as to whether or not this prohibition against transfusion is acceptable. If not, Jehovah's Witness patients should be referred or transferred to physicians who are willing to accept them. Time should not be wasted in misguided attempts to convince the Witness by argument and logic or in waiting for the situation to worsen in hopes the patient will convert at the operating room door. Unfortunately, we have seen just such actions rob actively bleeding patients of a chance for survival (3).

The adult Jehovah's Witness patient will usually identify himself or herself to treating physicians at the outset of the treatment encounter. Family members, or other church members, may tell the physician in an emergency if the patient is unable to do so. Witnesses also carry identification cards, advance directives, or other statements of their beliefs that specify their refusal of blood transfusion. Medical staff should look for such identification when treating an unconscious patient who is being considered for transfusion, since these cards, etc. have been upheld as legal and binding in United States courts (4). In *Malette v. Shulman*, the Court of Ontario established this precedent by awarding damages to a Jehovah's Witness who was transfused despite the fact that she had such a card (5,6).

What medical treatment does the Jehovah's Witness patient accept? There is a common misconception that they refuse any type of medical care. To the contrary, Jehovah's Witnesses actively seek the best in medical treatment. As a group, they are the best-educated consumers the surgeon will ever encounter and are knowledgeable, especially in areas of alternatives to transfusion. Their church has established local Hospital Liaison Committees, consisting of church members whose goals are to act as a liaison between the physician and the patient and to provide the physician with a clear understanding of the Witnesses' position, use of alternatives, etc (7).

In general, the Jehovah's Witness refuses any and all allogeneic blood products and any autologous blood that has been separated from the body for any length of time. The Watchtower has recently defined forbidden components as red blood cells, white blood cells, platelets, and plasma. All other components, such as cryoprecipitate, and alternative treatments are up to the individual to decide (Fig. 37.1). These prohibitions do not prevent the Witness from accepting the use of cardiopulmonary bypass, dialysis, and intraoperative blood salvage and reinfusion (8). From time to time, the Watchtower will publish guidelines concerning transfusion issues, with the instruction to the Jehovah's Witness that the decision to use an alternative is a matter of individual conscience. Such is the case with recombinant human erythropoietin (rHuEPO), which is manufactured using a small amount of human albumin. Albumin, when used as a volume expander, is considered an unacceptable blood product. Because the amount contained in rHuEPO is so small and the albumin is not intended for use as a blood product, it is acceptable. In our experience, only a small percentage of Jehovah's Witnesses have refused rHuEPO use.

Legal actions regarding Jehovah's Witnesses have helped define treatment approaches for the surgeon, particularly in controversial areas including transfusion of the minor, the use of emergency transfusion, and determinations of competency. Transfusion questions concerning minors usually only arise with children of Jehovah's Witnesses. Traditionally, the courts have ruled in favor of the physician in a decision to transfuse a minor, based on the doctrine of parens patriae, or the power of the state to preserve the lives of minors (9). However, times are changing as courts are beginning to distinguish between life-threatening and non life-threatening situations (10). More and more, physicians are being required to document the life-threatening nature of an illness and to justify the benefits of transfusion, i.e., to prove to the court that a transfusion will indeed be needed to save a child's life. In our experience, judges have required the physician to limit transfusion to the circumstances presented at the time of a court hearing and to report back to the court the success or failure of the transfusion. In other words, blanket orders *to transfuse as needed* are becoming rare. Similarly, if a surgical procedure is not needed to save a child's life and can safely be postponed until the child reaches adulthood, the court may deny such a procedure if it involves transfusion (11).

We believe that every effort should be made to avoid transfusion in Jehovah's Witness children to honor the beliefs the children often share with their parents. We support an approach to transfusion that includes anticipation of potential need coupled with detailed discussions with the parents of the circumstances and the possible outcomes before an emergency arises. In seeking a court order, you must be as specific as possible. For example, you are treating a 10-year-old boy with leukemia whose platelet count is drifting down after a round of chemotherapy. His hemoglobin is 7.4 gm per dL. You are treating him with intravenous iron and recombinant human erythropoietin. You are willing to let the platelet count drop to 10,000 before you transfuse. You discuss this plan with the parents before meeting with them and the appropriate judge to request an order that specifies *only* transfusion of enough single-donor aphaeresis platelets to maintain the platelet count above 10,000. The order is valid only for this transfusion and

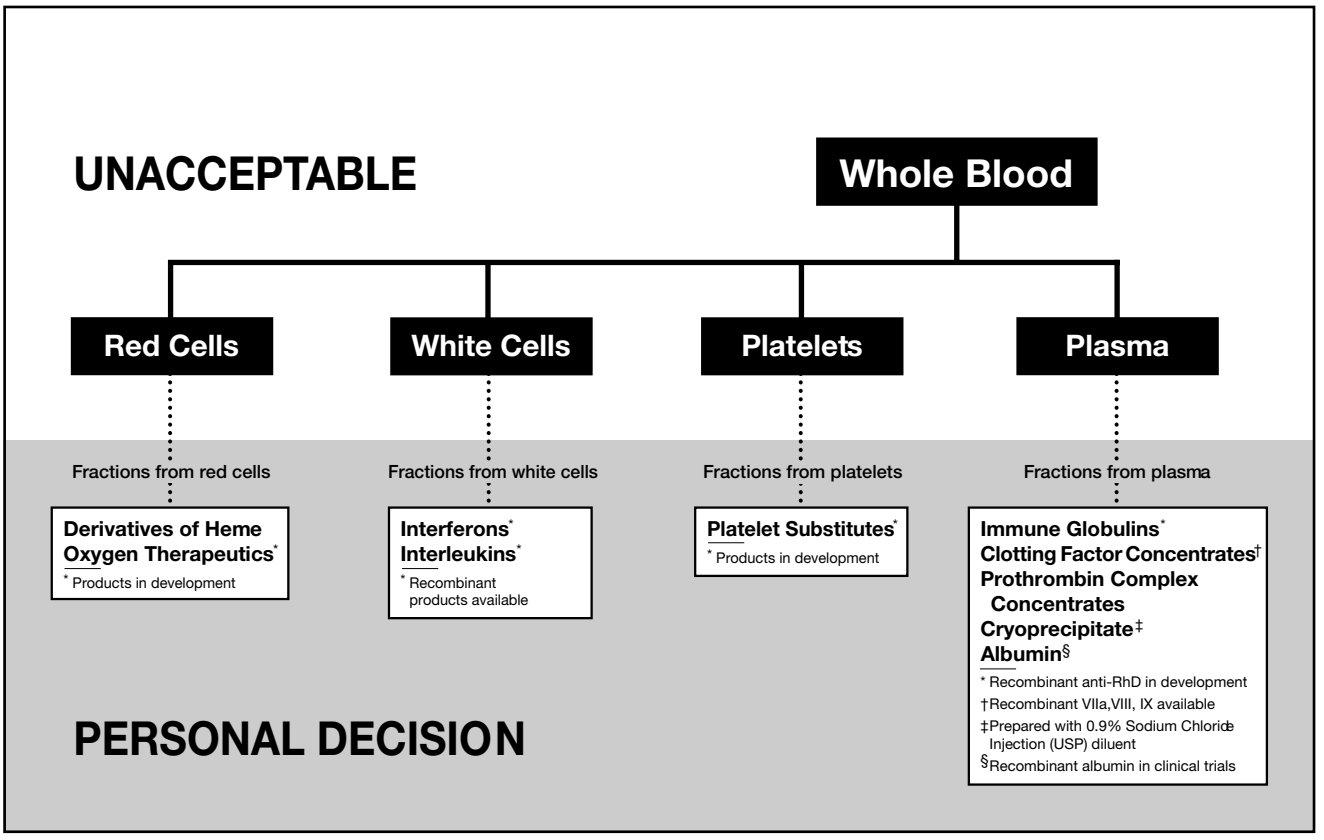

Figure 37.1 Individual Decisions Regarding Blood Transfusion.

requires you to report the child's response and clinical condition to the judge. You do not request a blanket order for transfusion of any other blood products. We have found that this approach recognizes and respects the parent's wishes while also protecting the child's life using the minimally necessary intervention.

The teenage patient, or mature minor, presents other problems to the surgeon. If a child has married, joined the armed forces, or has been legally emancipated, he or she is considered to be a competent adult with all attendant rights and privileges. Even without these factors, if the teenager is capable of understanding the nature and consequences of his or her actions, the courts may oppose a forced transfusion. The Illinois Supreme Court recently found in favor of a 17-year-old girl with leukemia who opposed a transfusion because of her religious beliefs (12). Luban and Leikin (10) suggest early open discussion with the parents of the Jehovah's Witness child and involvement of the patient when appropriate. The surgeon should consider how essential transfusion is to the patient's outcome and whether or not alternatives are available especially in light of the knowledge that a wide variety of surgical procedures, including those with unavoidable attendant blood loss, have been performed safely in Jehovah's Witness children using combinations of hemodilution, hypothermic anesthesia, and intraoperative salvage (13,14).

The prohibition against transfusion applies to the unconscious patient as well. Blood transfusion is acceptable in a life-threatening emergency if you do not know the patient is a Jehovah's Witness. However, if you do know, transfusion is not acceptable. Remember that deliberate failure to follow the Jehovah's Witness patient's wishes is grounds for a legal battery claim. In an emergency or when the patient is unconscious, the traditional approach is to stabilize the patient first, which may include the use of blood transfusion and to seek consent later. Most states will permit transfusion in this setting, provided there is no advance directive known to the physician prohibiting transfusion and the transfusion is needed to save the patient's life. One may need to be able to prove the latter after the fact.

Informed consent with the Jehovah's Witness, or for that matter, any other patient, should include a discussion of the potential of life-threatening hemorrhage and its consequences. This need to include such discussions has been made clear in two recent decisions regarding Jehovah's Witnesses. In a case similar to *Malette v. Shulman* discussed

above, the Michigan Court of Appeals ruled in favor of a surgeon who transfused his patient during a routine D&C when bleeding became life threatening (15). The decision to uphold the surgeon's actions was based in large part on the fact that the patient did not fully comprehend that she might die during the operation if a transfusion became necessary and was not given. In a similar case in New Jersey in which a patient bled during a hysterectomy, the surgeon sought a court order to transfuse on the basis of the inability to inform the unconscious patient contemporaneously of the change in circumstances, i.e., bleeding that now threatened her life. Given the life-threatening circumstances, the court allowed the husband to act as a surrogate and grant permission to transfuse, even though the patient was a known Jehovah's Witness. However, in their decision the court recognized that by failing to discuss the potential for life-threatening hemorrhage with the patient, the surgeon had not fulfilled his obligation to provide adequate informed consent. The appellate court subsequently upheld the decision while reaffirming the right of a Jehovah's Witness to refuse a blood transfusion while he or she is competent, or *when incompetent*, through an advance directive or living will. It is prudent; therefore, that surgeons discuss the *possibility* of life-threatening hemorrhage and the *possible* need for transfusion with all patients prior to surgery to assure that legally acceptable informed consent has been obtained. Remember that the patient's refusal to accept such a transfusion does not protect the surgeon from liability for any negligent actions that may necessitate transfusion.

The surgeon who does not feel comfortable treating Jehovah's Witness patients must know where to transfer them for medical care. There are many bloodless medicine and surgery centers that are willing to accept these patients. More often than not, the members of the Witness community know where these are and who to contact. Information also can be obtained from the Watchtower Society headquarters in Brooklyn Heights, New York, and from the Society for the Advancement of Blood Management (SABM) Web site that can be found at www.SABM.org. The physician's responsibility is to cooperate with the patient in facilitating a transfer. This is especially true with critically ill patients. This principle of "If you can't transfuse, transfer" is based on our experiences with preventable deaths in just such patients who were either treated inadequately, too late, or not at all.

The standard refusal of blood transfusion form in use in most hospitals typically is not comprehensive enough to cover all possible complications of surgery. Therefore, the surgeon should specifically document these in the record. In its 1988 report, The Presidential Commission on HIV recommended that all hospitals adopt reasonable strategies to avoid allogeneic transfusion including the use of alternatives (16). The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) now requires hospital staff to inform every patient at risk of transfusion about the risks and benefits of blood as well as available alternatives. The surgeon should check into what is available in his or her hospital and should analyze his or her practice to see where improvements can be made. If a patient is to be transferred to a Center for Bloodless Surgery or a sympathetic institution, arrangements should be made expeditiously to prevent unfavorable outcomes caused by ongoing bleeding. Our recommendations for dealing with the Jehovah's Witness patient are listed in Table 37.1.

GENERAL PRINCIPLES OF BLOODLESS MEDICINE AND SURGERY

Exposure of patients to allogeneic transfusion can be minimized or avoided by the systematic use of multiple blood conservation techniques. Such strategies exploit appropriate combinations of drugs, technological devices, and surgical/medical techniques. It also demands an interdisciplinary team approach, combining medical, surgical, and other specialists who share a commitment to avoiding the use of allogeneic blood transfusion. An overview of the general principles of medical and surgical care to minimize or prevent allogeneic transfusion is presented in Table 37.2.

The essential components that must be determined during the initial patient blood management assessment are the same for all patients. Information about hemoglobin, risk factors, treatment type, impact on RBC mass, and urgency of treatment are needed to plan the patient's transfusion alternative strategy. In addition to a history and physical examination focused on the presenting problem, the physician must investigate any preexisting conditions that may have an effect on both the planned treatment and the potential for blood transfusion. Preexisting conditions that are known to be risk factors for coronary artery disease include advanced age, elevated cholesterol, hypertension, chronic renal failure, smoking, peripheral vascular disease, and diabetes. Chronic obstructive pulmonary disease that limits oxygen exchange will have an impact on how well the patient is able to diffuse oxygen to red cells (17). Medications that modify coagulation such as nonsteroidal anti-inflammatory agents, aspirin, heparin, and warfarin must be investigated, since these can increase perioperative bleeding. The decision to discontinue these will be based on the patient's need for the drugs, the treatment planned, and its timing. The patient's hematological history should be obtained, asking about family history, previous surgery, dental extractions, and any associated bleeding diathesis.

TABLE 37.1
RELIGIOUS POSITION ON MEDICAL THERAPY

A: Acceptable Treatment

- Most surgical and anesthesiological blood conservation measures (e.g., hemostatic surgical instruments, controlled hypotension/hypotensive hemostasis, regional anesthesia, minimally invasive surgery, endovascular therapy, intraoperative positioning, maintenance of normothermia, meticulous hemostasis and surgical technique)
- Most diagnostic and therapeutic procedures (e.g., phlebotomy for laboratory testing, angiographic embolization)
- Pharmacologic agents that do not contain blood components or fractions such as:
  - Drugs to enhance hemostasis (e.g., tranexamic acid, epsilon-aminocaproic acid, aprotinin, desmopressin, conjugated estrogens)
  - Hematopoietic growth factors and hematinics (e.g., albumin-free erythropoietin, iron)
  - Recombinant products (e.g., albumin-free coagulation factors)
  - Topical hemostatic agents (e.g., collagen, gelatin-based hemostats, oxidized cellulose)
  - Synthetic oxygen therapeutics (e.g., perfluorochemicals)
  - Nonblood volume expanders (e.g., saline, lactated Ringer's, hydroxyethyl starches)

B: Personal Decision (Acceptable to Some, Declined by Others)

- Blood cell salvage* (intraoperative or postoperative autotransfusion)
- Acute normovolemic hemodilution*
- Intraoperative autologous blood component sequestration* (including intraoperative plateletpheresis, preparation of fibrin gel, platelet gel, platelet-rich plasma)
- Cardiopulmonary bypass†
- Apheresis†
- Hemodialysis†
- Plasma-derived fractions (e.g., immune globulins, antivenins, vaccines, albumin, cryoprecipitate‡)
- Hemostatic products containing blood fractions (e.g., recombinant factor VIIa§, coagulation factor concentrates, prothrombin complex concentrate, fibrin glue/sealant, hemostatic bandages containing plasma fractions, thrombin sealants)
- Products containing plasma-derived blood fractions such as human serum albumin (e.g., some formulations of erythropoietin, streptokinase, G-CSF, vaccines, recombinant clotting factors, nuclear imaging products)
- Products containing a blood cell-derived fraction, whether from a human or animal source (e.g., iron supplements, hematin, oxygen therapeutics, interferon alfa-n3 (leukocyte derived))
- Epidural blood patch
- Blood cell scintigraphy (e.g., radionuclide tagging for localization of bleeding)
- Peripheral blood stem cell transplantation (autologous or allogeneic)
- Transplants (organ, marrow, bone)

C: Unacceptable Treatment

- Transfusion of allogeneic whole blood, red blood cells, white cells, platelets, or plasma
- Preoperative autologous blood donation (PAD or predeposit)

* Patients might request that continuity is maintained with their vascular system
† Circuits not primed with allogeneic blood
‡ Cryoprecipitate suspended in 0.9% Sodium Chloride Injection (USP) diluent
§ Recombinant activated Factor VII contains trace amounts of IgG from the manufacturing process

Laboratory testing is not a substitute for this and should be used only to confirm a suspicion or to assess the status of anticoagulant therapy (18). Further evaluation by a specialist, especially in the area of congenital or acquired coagulation disorders, may be needed.

The patient's cardiopulmonary status is of utmost importance. Symptoms such as angina and dyspnea on exertion should be sought after. Details of any history of coronary artery disease, including recent myocardial infarction, surgery, or endovascular interventions must be obtained. Episodes of congestive heart failure have a negative impact on perioperative survival, independent of hemoglobin level (19). Be aware of medications that limit cardiac response, such as β-blockers. If the patient is not clear on details, these should be obtained from old records and/or the treating physicians. The primary concern in this

TABLE 37.2
GENERAL PRINCIPLES OF BLOODLESS MEDICINE AND SURGERY

Preoperative
1. Determine need for blood based on operation planned.
2. Assess all relevant medical history, current drug therapy, etc.
   a. Stop any drugs that may contribute to unwanted bleeding.
3. Assess hemoglobin/hematocrit early.
   a. If anemic, restore red cell mass with adequate nutrition, iron, and rHuEPO *before* surgery postponing surgery until this has been accomplished.

Operative Procedure
1. Choose procedure with least blood loss.
2. Use minimally necessary surgery, careful dissection, cautery, etc. to minimize blood loss.
3. Stop all bleeding, no matter how minor, when encountered.
4. Use anesthetic techniques designed to reduce blood loss.
5. Use drugs to prevent bleeding where appropriate, e.g., vasopressin, DDAVP, aprotinin.
6. Maintain circulating volume with asanguinous fluids.
7. Use hemodilution/autotransfusion where appropriate.

Emergency Surgery, or if Bleeding Actively
1. Resuscitate with asanguinous fluids.
2. Stop active bleeding nonoperatively where appropriate with:
   a. Endoscopic sclerosis or coagulation.
   b. Balloon tamponade.
   c. Angiographic embolization.
   d. Drugs.
3. Perform emergency surgery to stop bleeding if necessary.
4. Perform staged operation chosen to minimize blood loss.

Postoperative
1. Minimize phlebotomy.
2. Restore red cell mass with adequate nutrition, iron, and rHuEPO.

assessment is to determine if the patient can mount an appropriate response to existing or expected anemia. If there is any question, refer the patient to a cardiologist for assessment of functional status and fine-tuning of therapy.

You must know the hemoglobin or hematocrit (H&H) when you first see the patient. This is particularly true when planning for surgery. Ordering these values as preadmission tests and waiting until the morning of surgery to see them defeats the purpose of safe preoperative planning. You may be able to obtain the H&H from your hospital lab while the patient is in your office. If not, you can use a point-of-service office-based system such as the Hemocue to get a reliable hemoglobin measurement.

Some basics of dealing with hemoglobin levels apply to all patients. If the patient is anemic, you can get a good idea of the cause in most cases by checking the peripheral smear and red cell indices. If the patient is iron-deficient, remember to look for a source of bleeding. These may be related to the primary disease. Gastrointestinal or gynecological bleeding requires further investigation. Any unexplained anemia should be evaluated.

Oral iron therapy is the mainstay of treating iron deficiency anemia. There are many products on the market, most of them over the counter. Because iron is absorbed poorly from the gastrointestinal tract, response to treatment is slow. Therefore, therapy should be started early. If the patient is scheduled for elective surgery, the surgeon must adjust the date of the operation to allow for recovery of hematocrit. If urgent surgery is needed, intravenous iron replacement offers a means of increasing iron stores rapidly to stimulate erythropoiesis.

Any planned treatment must take into account its impact on the red cell mass. As is true of other patients, Jehovah's Witnesses are at most risk of anemia during surgical procedures with high blood loss and treatments such as chemotherapy that shut down erythropoiesis (20). Surgical procedures done with minimal blood loss, e.g., laparoscopic cholecystectomy, require no major intraoperative changes for Jehovah's Witnesses, unless they are anemic. In these patients, iron and recombinant human erythropoietin (rHuEPO) therapy can restore the red cell mass to normal before surgery. The decision to use preoperative treatment will depend on the patient's overall condition as well as the

degree of anemia. However, if the planned surgical procedure frequently leads to blood loss and allogeneic transfusion, then the surgeon will need to plan for alternatives to allogeneic blood. The only way to know if the operation planned leads to blood loss and transfusion is to gather and review personal data. The information need not be complex, but it must include the variables that play a role in the transfusion decision. This database must be an active instrument that can be revisited and analyzed periodically to understand changes in transfusion practice. Periodic record review will also help identify those patients that would benefit from alternatives. Chapter 44 on blood management strategies in the patient with cancer provides excellent guidelines for treating the Jehovah's Witness oncologic patient.

Multiple alternatives to allogeneic blood are discussed in detail in this text. Most are applicable to all patients; however, some are not acceptable to the Jehovah's Witness patient. Most Witnesses accept preoperative therapy with iron and rHuEPO although some may refuse the latter because of concerns over the small amount of human albumin used in the manufacturing process. Be sure to get the patient's consent before using rHuEPO. A simple measure to conserve the patient's own blood consists of restricting phlebotomy (reducing the number of tests and the volume of blood withdrawn) (21). Another measure is careful management of anticoagulation, including discontinuation or substitution of agents that could adversely affect clotting in the perioperative period (e.g., ASA and medication containing aspirin, NSAIDs, antiplatelet agents, anticoagulants).

Autologous predonation (PAD) has been used for several years in orthopedic, urological, and cardiac surgery to reduce the use of allogeneic blood. Jehovah's Witnesses do not accept predonation of their own blood because of the physical separation, storage, and possibility of a mismatched transfusion. Acute normovolemic hemodilution (ANH) is an alternative to PAD that eliminates many of the objections to the use of autologous blood. Acute normovolemic hemodilution is the process of removing and temporarily storing blood just before or immediately after the induction of anesthesia and replacing volume losses with either crystalloid or colloid solutions (22). Most Jehovah's Witness patients will accept ANH if the blood is collected in a closed system; that is, one in which a continuous circuit is maintained between the phlebotomy site and the intravenous infusion site. This can be done easily with the use of preconnected donor bags, tubing, and three-way stopcocks. Most Jehovah's Witnesses also accept intraoperative autotransfusion, or cell salvage, during surgery if a closed circuit is used. It is essential to obtain the patient's consent for both ANH and autotransfusion because both of these are considered a matter of conscience.

The principles of surgical and anesthetic bloodless management are summarized in Table 37.2. The sine qua non of reducing transfusion need in surgical patients is to prevent blood loss. Surgeons are trained in the art of gentle tissue handling, recognition and avoidance of potential bleeding sources, and rapid control of unexpected hemorrhage to accomplish this goal. Traditionally, minor bleeding has been prevented with electrocautery, utilizing either monopolar or bipolar instruments (23). Newer modifications to electrocautery include argon beam-enhanced, ultrasound, and microwave cautery devices (24,25).

Tissue, or fibrin, sealant products are combinations of purified thrombin and fibrinogen from either human or animal sources that reproduce the last states of the coagulation cascade; that is, the conversion of fibrinogen into fibrin monomers and the cross-linking of these into an insoluble fibrin matrix (26). The sealants typically are provided in two syringes, the first containing concentrated fibrinogen and aprotinin; the second containing thrombin and $CaCl_2$ in equal parts. A variety of mixing tips are available to permit pinpoint or spray application to a cut or bleeding surface. These products have been shown to reduce both blood loss and transfusion need in a wide variety of surgical procedures. Some Jehovah's witnesses may not accept products that contain human thrombin.

Pharmacologic and mechanical blood conservation procedures are valuable adjuncts but cannot replace rigorous hemostasis and good surgical technique. Performing complex elective procedures in stages (also termed *planned reoperation* or *staged procedure*) may minimize blood loss in specific clinical situations (27). In the Jehovah's Witness patient who is actively bleeding from trauma, emergency surgery must be performed to control hemorrhage. We have previously demonstrated that rapid control of bleeding is a critical factor in improving survival, especially in the Jehovah's Witness. Definitive repair of associated traumatic injuries can be done after bleeding is stopped and the patient is stabilized. Later, a planned reoperation can be performed more safely for definitive repair of injuries. For elective operative procedures with an expected, high blood loss, staged surgery should be part of an overall blood conservation strategy (24).

The use of controlled hypotensive anesthesia, maintenance of normothermia, blood cell salvage, and tolerance of normovolemic anemia are all associated with reduced surgical blood loss. Data suggest that each can contribute to reduction of bleeding (28). Patient positioning is a simple measure that involves elevating the surgical site to reduce arterial pressure and facilitate venous drainage away from the surgical wound (29). Care must be applied not to introduce air into the venous circulation.

Methods relevant to the immediate postoperative period include close surveillance for bleeding, adequate oxygenation, restricted phlebotomy for diagnostic tests, pharmacologic enhancement of hemostasis, avoidance of hypertension, meticulous management of anticoagulants

and antiplatelet agents, and tolerance of normovolemic anemia. The hemoglobin-based *transfusion trigger* has evolved over time from a level of 10 gm per dL to 7 gm per dL with an increasing emphasis on clinical assessment. However, several studies show that patients are able to tolerate lower hemoglobin levels than previously believed (30,31). A randomized controlled trial involving 838 normovolemic critically ill patients demonstrated that a restrictive red cell transfusion strategy (hemoglobin level between 70 and 90 g per L) was as safe as a liberal transfusion strategy (hemoglobin level between 100 and 120 g per L) in critically ill patients, with the exception of patients with ischemic cardiovascular disease (30). Reports of successful surgery, ranging from the simple to the complex, done in Jehovah's Witnesses without transfusion attest to the safety of tolerating a degree of postoperative anemia (32–34).

Although the alternatives discussed above can be used individually with success, they are most effective when employed together in a blood management strategy that is individualized to a specific patient. For example, a patient scheduled for an elective joint replacement surgery that typically leads to a two-unit red cell transfusion should be assessed several weeks before surgery to look for anemia or iron deficiency. If present, these can be corrected with the use of iron and erythropoietin therapy to increase hematocrit, thereby improving the patient's tolerance to anticipated blood loss. The use of ANH can reduce the number of shed red cells per unit volume, thus decreasing red blood cell volume lost. Shed blood can be collected and reinfused during surgery. Tolerance of postoperative anemia while accelerating erythropoiesis with iron and rHuEPO rounds out the strategic plan (35).

The value of combining alternatives has been proven in a series of 100 consecutive patients, including Jehovah's Witnesses, who underwent coronary artery bypass grafting without the use of blood. Mortality in this group was 4%, which is comparable to large series of similar patients who received blood (36). The key to success in this series was the use of multiple alternatives—iron, erythropoietin, cell salvage, ANH, careful surgical technique, lowered transfusion trigger—and commitment of all the treating personnel.

In conclusion, there are a number of safe and cost-effective therapeutic options for the potential management of Jehovah's Witness patients without allogeneic blood transfusion. Physicians should consider blood management using these options for *all* patients.

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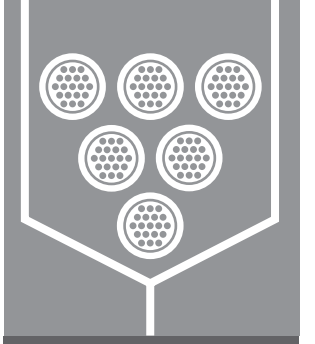

38

Coagulation, Transfusion, and Cardiac Surgery

Simon C. Body *David S. Morse*

Nowhere in the practice of medicine, do alterations in the coagulation state occur with such planned severity as during cardiac surgery. Indeed, they are vital. Over the last decade we have seen sweeping advances in preoperative anticoagulant and antiplatelet therapies for myocardial ischemia and infarction that have direct impact on the management of coagulation disorders after bypass. Yet, heparin and heparin alternatives are still essential for the practice of cardiopulmonary bypass (CPB). In addition, the management of perioperative coagulopathy and bleeding with routine antifibrinolytics has undergone considerable change. Although advances in therapies for CPB-induced fibrinolysis and improved safety of the blood supply have brought changes to the practice of cardiovascular surgery, the postoperative hypocoagulable and hypercoagulable states are still everyday clinical conundrums facing the surgeon, anesthesiologist, and intensivist. Other important areas of study and controversy surrounding cardiac surgery include the appropriateness of reduction in variability in allogeneic blood product transfusion, management of anticoagulation and coagulation during CPB, management of patients with specific hematological disorders, the significance of the multitude of inflammatory changes that occur during and after CPB, and genetic, and other, predictors of bleeding outcomes.

NORMAL PHYSIOLOGY OF THE COAGULATION SYSTEM

Hemostasis occurs along two, usually concurrent, phases. The first phase, primary hemostasis, occurs when platelets adhere to areas of intimal damage or loss to form a platelet plug. The second phase, secondary hemostasis, occurs when the platelet activates the coagulation cascade. Several components and products of normal vascular endothelium prevent platelet adherence and binding to endothelium. These include the heparins, nitric oxide, prostaglandins, thrombomodulin, prostacyclin, tissue plasminogen activator, and endonucleotidases. Injury to the endothelium allows platelets to adhere to the damaged area. In the normal situation, platelets interact or roll along the vessel wall, exposing platelet receptors to the endothelium. When the endothelium is damaged or lost, these platelet receptors adhere to the subendothelial matrix. Principally, platelet glycoprotein lb binds to vWF of the matrix. Circulating vWF can also bind matrix collagen, acting as a bridge between the platelet and the matrix. Collagen and other matrix adhesion (glyco) proteins, vitronectin, fibronectin, and thrombospondin also bind to platelet membrane proteins to facilitate platelet adhesion.

The adhesion event causes several platelet changes; notably activation and degranulation. Dense and α-granules are fused with the platelet wall and release their contents, consisting of ADP, fibrinogen, vWF, fibronectin, vitronectin, thrombospondins, and other factors. Platelet ADP binds to its own platelet membrane receptors to induce a further sequence of events, including shape change (via actin filaments) and exteriorization of the glycoprotein IIb/IIIa receptor, which binds fibrinogen (Fig. 38.1). Fibrinogen acts as the cross-link between platelets and is the primary mechanism of platelet aggregation and recruitment. Platelet phospholipases are also activated to manufacture and release thromboxanes. These cause vasoconstriction, altering shear stress,

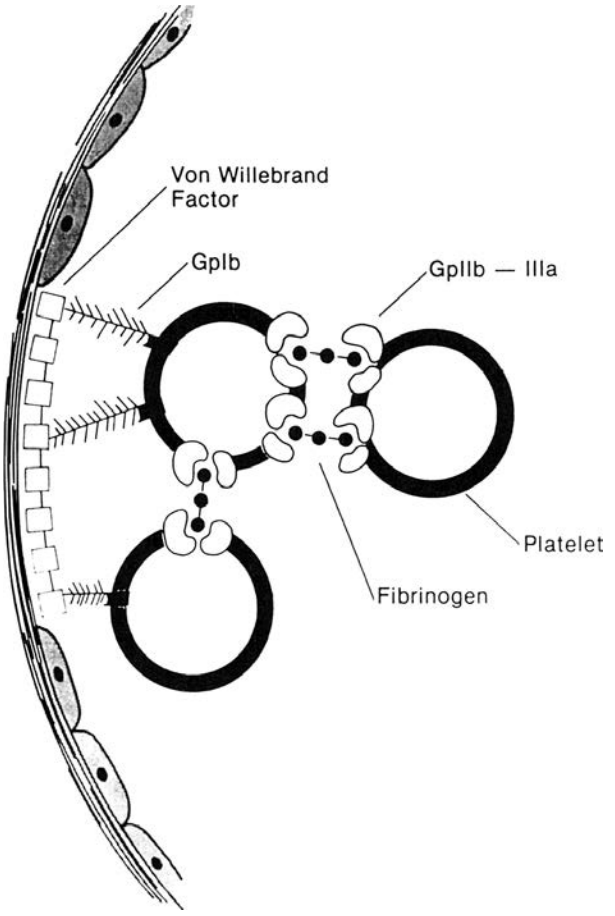

Figure 38.1 Molecular mechanism of platelet attachment to the vascular subendothelium (platelet adhesion) and of platelet–platelet adhesion. (Reprinted with permission from Handin R, Loscalzo J. Hemostasis, thrombosis fibrolysis and cardiovascular disease. In: Braunwald E, ed. *Heart disease. A textbook of cardiovascular medicine.* 4th ed. Philadelphia, Pa: WB Saunders; 1992: 1767–1789.)

the washout or dilution of platelet products (ADP and others), and also directly recruit and activate platelets in the platelet plug.

MECHANICS OF THE CPB

During cardiac surgery, the CPB pump customarily replaces the function of the heart and lungs. The pump is usually primed with a crystalloid solution unless the patient is unusually small or anemic. Heparin is sometimes added to the pump prime, in addition to direct administration to the patient. After placement of drainage (venous) and return (arterial) cannulae and assurance of adequate heparinization, CPB is commenced by allowing the blood to drain from the patient via the venous cannula to the pump and after oxygenation is then returned to the patient. CPB is usually conducted with systemic flows of 1.0 to 2.2 L per min.m^{-2} and systemic pressures of 40 to 80 mm Hg at temperatures of 25°C to 37°C. In the last decade we have seen a much greater use of tepid bypass at temperatures of 33°C to 35°C.

The path of blood within the bypass pump is as follows (Fig. 38.2). Venous blood from the right atrium or vena cavae is drained by gravity into an enclosed reservoir. The reservoir provides a buffer volume to account for variations in drainage of venous blood from the heart. In a so-called, and almost extinct, bubble oxygenator it also forms part of

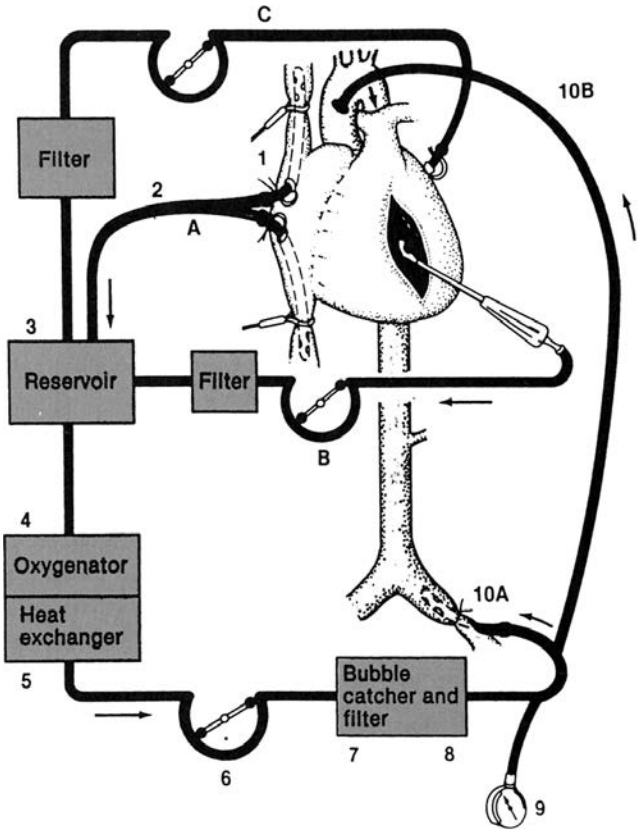

Figure 38.2 Schematic diagram of a cardiopulmonary bypass pump, bubble oxygenator, and circuit. Blood is drained by gravity from the vena cavae (1) through the venous cannula (2) into the venous reservoir (3). Heparinized blood from the surgical field and cardiotomy vent sites are pumped (B) to the venous reservoir (3). For circuits using bubble oxygenators, the blood is oxygenated (4) and then either heated or cooled (5), as appropriate, and pumped (6) back to the patient through a filter (7, 8) that can also act as a bubble trap. For membrane oxygenators, the order of the pump and oxygenator is reversed. The pressure in the arterial line is monitored (9). Blood can be returned to the patient via either the femoral artery (10A) or aorta (10B) or another arterial site. (Reprinted with permission from Antman E. Medical management of the patient undergoing cardiac surgery. In: Braunwald E, ed. *Heart disease. A textbook of cardiovascular medicine.* Philadelphia, Pa: WB Saunders; 1992:1670–1693.)

the oxygenator circuit. In addition, heparinized blood collected on the surgical field can also be suctioned back to the reservoir. The reservoir usually contains a macro filter (170 μm or similar) to filter foreign debris or particulate material before the suctioned blood is allowed to mix with the venous drainage blood from the patient.

From the reservoir, the blood is pumped, using either a roller pump, or centrifugal or vortex pump, to the membrane oxygenator. The roller pump is composed of two rollers, 180° apart, compressing flexible plastic or rubber tubing contained within a metal raceway. Each roller, as it rotates, compresses the tubing, almost completely, forcing blood along the tubing. As one roller disengages from the raceway, the other roller engages, giving a continuous flow with only minor flow and pressure fluctuations. Centrifugal pumps are cone-shaped pumps containing an impeller that spins at high speed, forcing the blood outward, similar to water being thrown off an automobile tire. The pump is driven by an electric motor through a magnetic coupling. In bubble oxygenators, the pump is placed downstream from the oxygenator; in contrast, membrane oxygenators have a high resistance and the pump is placed upstream from the oxygenator so that higher pressures can be generated to push blood through the oxygenator.

Membrane oxygenators separate the blood phase and gas phase using a thin (approximately 25 μm) membrane, through which oxygen and carbon dioxide diffuse. The membrane itself can be a thin sheet or, more typically, a hollow fiber composed of polypropylene. Other materials used are Teflon or polydimethylsiloxane. Most commonly, the gas is contained within the fiber and blood is allowed to circulate outside the wrapped fibers. The total surface area varies from 1 to 5 m2, depending on the manufacturer and intended use of the pump (pediatric versus adult). The diffusion constant for oxygen through polypropylene is considerably less than that for carbon dioxide, hence the large surface area. Bubble oxygenators simply bubble a continuous stream of oxygen or an oxygen–air mixture throughout the blood contained in the hard-shell reservoir. Gas transfer is usually efficient and adequate for routine CPB. However, the gas–blood interface is a powerful stimulus to platelet and neutrophil activation as well as complement activation and their use is almost died out.

Within the reservoir or oxygenator, the blood can be cooled or heated by the passage of water through stainless steel or aluminum alloy pipes, around which the blood flows. Most institutions place a 20-μm to 40-μm arterial filter in the outflow of the oxygenator to trap microemboli consisting of air, thrombus, fat, fibrin, foreign particles from the pump and circuit, and other debris. The blood is finally returned to the patient via the arterial cannula, usually placed in the ascending aorta.

Ventricular Assist Devices

Ventricular assist devices are designed to temporarily replace the function of either the right or left ventricle. Most commonly, they are placed on the left side of the heart and drain blood from the atrium or ventricle and pump it back into the ascending or descending aorta or the femoral artery. There is no oxygenator function to these devices. The pumping system can be either a roller or centrifugal pump or a valved, air-driven, bladder pump. Heparinization is initially required for their implantation on CPB, but their small and deliberately nonreactive surface area usually means that continued anticoagulation with warfarin or aspirin is adequate to prevent thrombosis.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is functionally similar to CPB but is used to provide long-term cardiac and pulmonary support, usually for pulmonary failure. Its efficacy is limited by the irreversibility of many diseases and the high rate of complications, usually hemorrhagic, renal, and cerebral. Structurally, the bypass system has many similarities to CPB, but the venous and arterial access points are often percutaneous. Systemic heparinization is required but usually at reduced levels compared with those for CPB. ECMO appears to have most utility in the neonatal population, principally for respiratory distress of the newborn, meconium aspiration, and after cardiac or pulmonary surgery.

PATHOPHYSIOLOGY OF CPB

The initiation and maintenance of CPB require several components that alter coagulation and humoral function: heparinization, air and foreign surface exposure, hemodilution, hypothermia, nonpulsatile flow, and protamine administration. These changes induce a multitude of barely understood effects that have been described as an inflammatory response, involving the formed blood elements, coagulation, complement, and kallikrein/kinin systems. The most immediate changes in the formed blood elements are induced by hemodilution. The CPB pump is primed with crystalloid solution, or rarely with colloids or blood. Depending on the blood volume and the volume of the priming solution, there is usually a reduction in hematocrit, white blood cell count, and platelet count by approximately 40%. Further reductions in the platelet count typically occur, and depend on the volume of suctioned blood, degree of hypothermia, adherence of platelets to the bypass pump components, and destruction of platelets by the bypass pump.

Hypothermia

Local and/or systemic hypothermia increases bleeding in the surgical patient. Cardiac surgeons and anesthesiologists have noted that rewarming the patient fully after systemic hypothermia reduces postoperative blood loss (1). Animal studies have shown that hypothermia to 20°C causes thrombocytopenia because of hepatic platelet sequestration and increased fibrinolysis (2). Local hypothermia causes an increase in the bleeding time and a decrease in platelet production of thromboxane B_2 in the blood shed during a bleeding time test. These changes are reversed, albeit incompletely, by rewarming to 37°C (3).

These animal observations have been confirmed in humans. The bleeding time in humans undergoing systemic hypothermia on CPB to 25°C is prolonged (4). Furthermore, comparing the bleeding time in one arm of a patient with a systemic temperature of 25°C with the other arm (kept warm to 35°C by a local warming blanket), the cold arm has a prolonged bleeding time with lower shed thromboxane B_2 concentrations than the warm arm. Systemic hypothermia has also been shown to reduce neutrophil activation and the generation of C3a/C5a. CPB temperatures of 27°C to 28°C are associated with increased release of P-selectin (a marker of platelet activation) compared with 36°C.

The benefits of systemic normothermia on coagulation must be balanced against the theoretical protective end-organ effects of moderate or deep hypothermia (1). A majority of studies investigating neurologic function in the context of bypass temperature find an increased incidence of stroke and cognitive dysfunction after normothermic (>35°C) versus moderately hypothermic CPB (5,6).

Blood Interaction with the Foreign Surface of the CPB Circuit

The use of CPB during cardiac surgery inevitably results in humoral, hematological, and coagulation disturbances caused by blood contact and flow disturbances within the extracorporeal circuit. All types of oxygenators cause damage to the cellular and noncellular elements of the blood. The damage is greatest at the blood–gas and blood–surface interfaces but can occur without foreign–surface interaction because of shear rate injury to the blood. Proteins are denatured and may circulate (bubble and membrane) or adhere (membrane) to the oxygenator surface. In the United States and Europe, membrane oxygenators are now used almost exclusively. Reasons for this practice include concerns for blood trauma, hemolysis, activation of inflammatory mediators, systemic microembolization, and need for defoaming agents when bubble oxygenators are used.

In general, in vitro tests of oxygenators and the associated hardware demonstrate less injury to formed blood elements with membrane than with bubble oxygenators (7). This is likely because the blood–gas interface is larger with a bubble oxygenator. For example, although bubble oxygenators tend to cause less initial platelet binding, the air–blood interface eventually results in more platelet activation over time than the surface of a membrane oxygenator. Platelets are sensitive to damage during CPB and thus serve as good intermediate outcome markers. Changes in platelet numbers, morphology, and receptors occur early in CPB, prior to evidence of other cellular injury. Overall, membrane oxygenators are associated with less trauma and sequestration of the formed elements, less platelet activation, and better platelet preservation both in vitro and in clinical trials (7,8). Hemolysis and granulocyte activation are also less extensive with membrane oxygenators (9).

However, markers of cellular and noncellular damage represent only intermediate outcomes. More appropriate outcomes to examine are blood product requirements, the incidence and severity of end-organ dysfunction and the duration and cost of hospitalization. These are seldom well examined in most studies. When examined, the difference in blood transfusion requirements between the two oxygenators on blood loss is minimal; several studies have failed to demonstrate reductions in blood loss with membrane oxygenators (7,10). However, other studies have demonstrated clinical advantages of membrane oxygenators for longer perfusion periods (9,11).

Bubble oxygenators result in the occurrence of gaseous microembolization. Bubble oxygenators use defoaming agents to reduce air microemboli. However, the efficacy of these agents is incomplete at best. Studies using Doppler ultrasound analysis at the level of the arterial cannula and at the middle cerebral artery (12) show reduction, if not elimination, of microemboli attributable to gaseous bubbles with membrane as opposed to bubble oxygenators. Retinal angiography similarly shows substantial reduction in the incidence and extent of retinal microemboli in patients undergoing CPB with membrane oxygenators (13).

Complement Activation and Its Modulation

Complement constitutes a major part of the body's response to trauma, infection, or immunological stress. The classical pathway is most commonly initiated by antibody–antigen complexes, whereas the alternative pathway is initiated by foreign bodies or surfaces and by various microbial organisms. Both classical and alternative pathways are initiated by circulating lipopolysaccharides/endotoxin and by tissue injury (14). In addition to the two earlier described pathways, the lectin pathway has been described (15). Mannose-binding lectin (MBL) recognizes glycoproteins found on bacterial cell walls and sometimes to self-membrane glycoproteins. MBL is complexed to MBL-associated serine

proteases (MASPs) (16). When MBL binds to nonself glycoproteins it causes activation of MASPs leading to cleavage of complement proteins and triggering of the complement cascade. Deficiency of MBL is a risk factor for infection, but MBL has a potential to react against self glycoproteins, such those found on apoptotic or ischemic-reperfused cells (17). Increased levels of MBL, seen with some haplotypes of the MBL gene, predispose to increased risk of thrombotic events (18) and the severity of myocardial infarction after a standardized ischemic insult (19).

Complement activation is a ubiquitous aspect of CPB, with involvement of all three pathways (Figure 38.3). The alternative and lectin pathways are activated by the surface of the circuit and oxygenator, (20) although surface activation of factor XII may also activate C1 and initiate the classical pathway (21). Trauma to formed blood elements activates the alternative and lectin pathways, whereas denatured immunoglobulin aggregates, seen with blood–gas interfaces, activate the classical pathway (22,23).

Increases in the levels of the complement fragments C3a and the C5b-9 membrane attack complex are observed on bypass (24,25). Most, but not all, studies fail to detect an increase in C4a, indicating predominance of the alternative pathway in complement activation (26,27). C5a, although undoubtedly present on bypass, is difficult to detect because of its rapid binding to neutrophils (24).

The oxygenator (or any foreign surface) plays a primary role in the hematological and inflammatory changes of bypass. For example, membrane oxygenators use does not completely remove the direct blood–gas interface (7). Moreover, membrane oxygenators with a high surface area may result in increased complement activation via the alternative pathway (28). Some studies have shown no difference in total complement activation between different categories of oxygenator (8). However, studies comparing bubble with membrane oxygenators have been hampered by variation in degree of hypothermia, hemodilution, heparin dosage, and priming solution (29,30). These variables greatly affect complement activity. In addition, membrane oxygenators are quite heterogeneous, varying in materials, surface area, flow patterns, and porosity (23,31). It is not surprising, therefore, that such comparisons are inconclusive (20,32).

Protamine infusion causes complement activation in the postbypass period. Although protamine alone has no effect

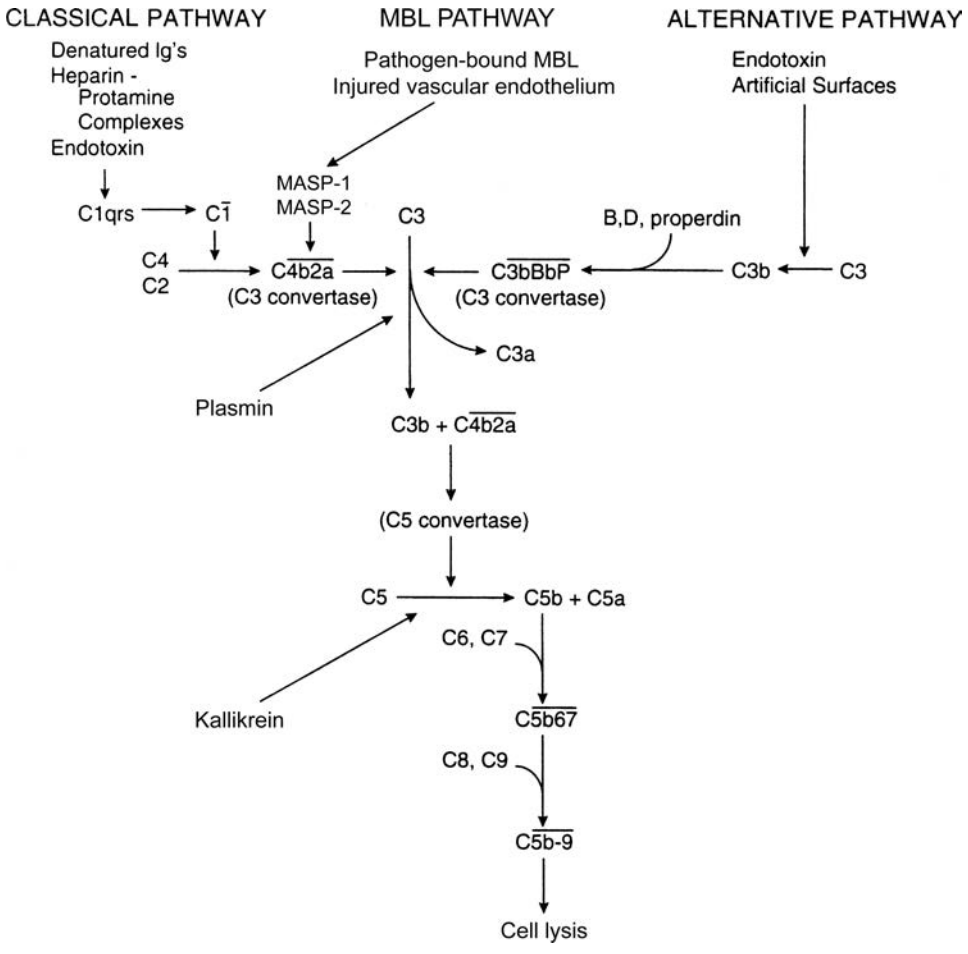

Figure 38.3 Complement activation during CPB. (Modified by permission from Warren J, Ward P, Johnson K. The inflammatory response. In: Williams WJ, Beutler E, Erslev AJ, et al., eds. *Hematology.* New York, NY: McGraw-Hall; 1990: 63–70.)

on complement, heparin–protamine complexes activate the classical pathway with production of C3a, C4a, and C5a (20,32). The products of complement activation, particularly the anaphylatoxins C3a and C5a, result in pulmonary sequestration of neutrophils, increased capillary permeability, vasoconstriction, and cardiac, pulmonary, and renal dysfunction (33). The acute lung injury associated with bypass-induced complement activation is often referred to as the postpump or postperfusion lung syndrome. The pattern of injury involves an initial transient hypoxemia associated with an increase in pulmonary vascular resistance followed by a sustained increase in pulmonary capillary permeability and lung water, resulting in a syndrome resembling adult respiratory distress syndrome (34).

After restoration of pulmonary blood flow, neutrophil counts decrease across the pulmonary vasculature and increase peroxidation products and transvascular protein flux (34,35). This dysfunction is a result of complement activation of neutrophils, which adhere to endothelium and produce oxygen-free radicals, peroxidase products, and arachidonic acid metabolites (32,36). These activation products cause increased pulmonary vascular resistance and decreased arterial oxygenation, which are ameliorated by cyclooxygenase inhibitors and/or free radical scavengers (37).

Inhibition of complement activation involves measures to directly inhibit complement formation (e.g., membrane oxygenators, heparin-coated circuits, aprotinin, soluble complement inhibitors) or measures to modulate the effects of complement on leukocytes and leukocyte-based mediators of injury (e.g., steroids, prostaglandins, thromboxane antagonists) (Figure 38.4). Heparin has been shown in vitro to inhibit complement activation by both classical and alternative pathways (38). Biocompatible circuits are designed to minimize activation of complement (and other inflammatory mediators) by coating the bypass circuit, oxygenator, or both with heparin. Studies comparing heparin-coated with noncoated surfaces have investigated complement activation, neutrophil activation, cytokine release, and pulmonary function with unclear results. Some show heparin-coated circuits to decrease, but not eliminate, activation of C3 on bypass (38,39). However, others show no change in C3 activation or a change that occurs only after bypass as a result of decreased protamine dose requirement (40,41). Similar confusion exists with regard to C5 activation. C5a binds rapidly to neutrophils and is thus difficult to assay (38). Studies that attempt to measure C5a or C5b-9 as a surrogate for C5 activation have had equivocal results with regard to heparin-coated circuits (38,42). Similarly equivocal results have been seen with regard to the effect of coated circuits on production of interleukin-6, interleukin-8, and other markers of leukocyte activation (43).

Aprotinin, the naturally occurring inhibitor of kallikrein and plasmin, has been proposed as an inhibitor of complement activation. In vitro, aprotinin reduces C1 activation at

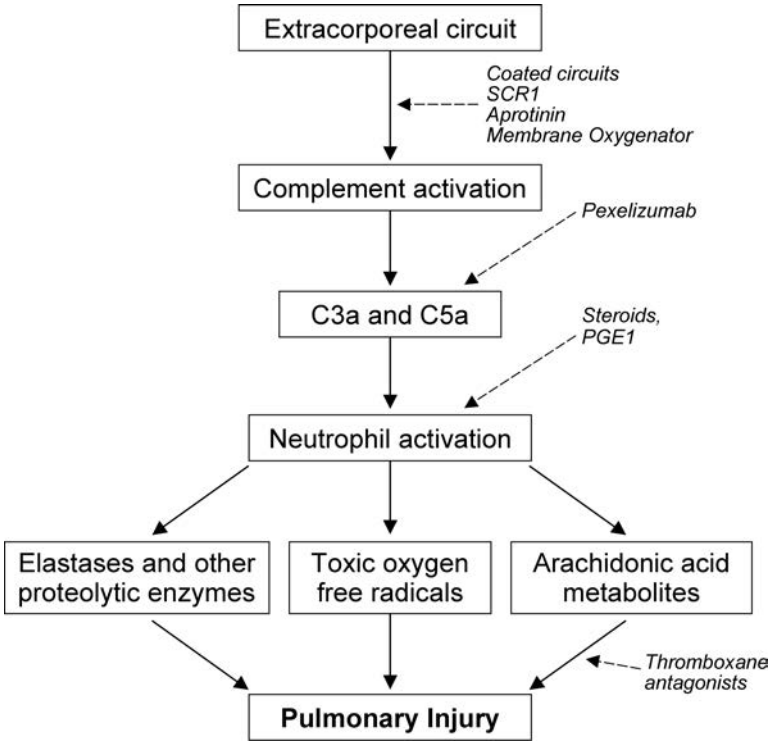

Figure 38.4 Approaches to prevention of complement-induced pulmonary injury during CPB. (Modified with permission from: Oster JB, Sladen RN, Berkowitz DE. Cardiopulmonary bypass and the lung. In: Gravlee GP, Davis RF, Kurusz M, et al., eds. *Cardiopulmonary bypass: principles and practice.* Philadelphia, Pa: Lippincott Williams & Wilkins; 2000.)

kallikrein-inhibiting doses and partially inhibits neutrophil elastase release (21). This is not likely to be a direct effect of aprotinin but a result of inhibition of kallikrein, plasmin, and factor XII. Aprotinin has no effect on generation of factors C3a or C4a in vivo.

Soluble complement receptor type 1 is a recombinant form of the membrane-bound complement inhibitor found on formed blood elements. An inhibitor of both the C3 and C5 convertases, it inhibits complement activation by both the classical and alternative pathways. In a porcine model of CPB, soluble complement receptor type 1 eliminated activation of C3 and C5 (22). However, little effect was seen on neutrophil activation, pulmonary edema, or arterial oxygenation.

Alternatively, a short-acting monoclonal antibody against C5 (pexelizumab) has been shown to dose dependently reduce production of the terminal complement complex (C5b-9) without effect on C3a in patients undergoing CPB. In theory, this inhibition at the level of the C5 convertase preserves the antibacterial activity of C3 derivatives while targeting the deleterious inflammatory effects of C5a and the terminal complement complex (44). One study has found that clinical effects of this inhibitor include reduced leukocyte activation, rate of myocardial infarction, and neurologic deficit (45). Other studies, however, have shown minimal clinical benefit (44). This drug shows promise for future investigation and use.

Modulation of complement effect on neutrophils and the pulmonary vasculature without direct complement inhibition has been attempted with steroids, prostaglandins (PG), specifically PGE_1, and thromboxane antagonists. In general, steroids have not been shown to reduce complement activation on bypass (46). In one study, methylprednisolone reduced C3a activation by bubble oxygenators, but not by membrane oxygenators (47). However, steroids have been variously reported to reduce pulmonary sequestration of neutrophils, to reduce generation of tumor necrosis factor and leukotriene B4, to reduce pulmonary vascular resistance and hypoxemia, and to reduce postoperative complications and intensive care unit duration (30,46,48). Given the general lack of confirmation and a number of contradictory studies, routine steroid use does not seem justified.

Kallikrein Function and Its Modulation

Kallikrein is activated from prekallikrein as part of the intrinsic or contact-activated coagulation pathway. It is a significant mediator of the "whole-body inflammatory response" to CPB (49). Polyanionic surfaces such as subendothelial collagen or foreign surfaces, such as the bypass oxygenator and circuit, bind prekallikrein and high-molecular-weight kininogen, bringing these two proenzymes into proximity with activated factor XII (50). Factor XIIa converts prekallikrein to kallikrein, which correspondingly activates additional factor XII (Figure 38.5). This positive feedback loop provides physiological amplification of the clotting cascade.

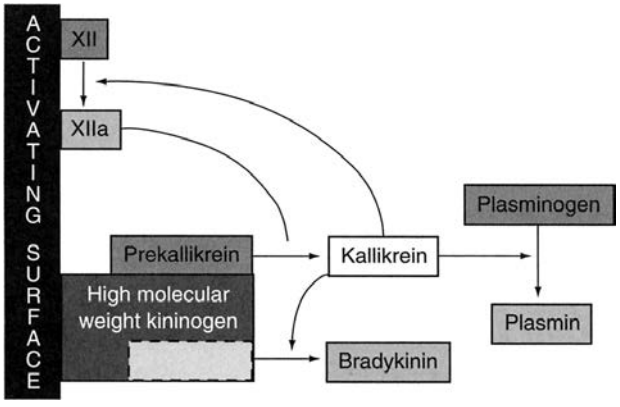

Figure 38.5 Role of kallikrein in surface activation.

Kallikrein converts high molecular weight kininogen to bradykinin, which increases microvascular permeability and dilates arterioles, contributing to hypotension and pulmonary dysfunction in settings ranging from endotoxin shock to CPB (51). Bradykinin is metabolized by a converting enzyme associated with the pulmonary vascular endothelium. Consequently, exclusion of the pulmonary circuit during bypass leads to reduced metabolism, in addition to increased production of bradykinin (52). The degree of bradykinin generation appears to vary with time of bypass, depth of hypothermia, and composition of pump prime (51).

More importantly, kallikrein leads to generation of plasmin from plasminogen, which in the setting of CPB quickly overwhelms its circulating inhibitors. Plasmin activates and aggregates platelets, rendering them susceptible to clearance from the circulation or, if uncleared, unable to participate in the release reaction (53). Plasmin cleaves platelet surface receptors for adhesion (glycoprotein Ib) (54,55) and aggregation (glycoprotein IIb/IIIa) (56). Finally, it metabolizes fibrin to fibrin degradation products that interfere with platelet aggregation and fibrin cross-linking. None of these effects taken alone are sufficient to produce abnormal clotting. However, taken together, these events, with plasmin as a common catalyst, contribute significantly to the multifaceted hemostatic defect seen after bypass.

Endogenous kallikrein modifiers include the C1 inhibitor, α_2-macroglobulin, α_1-antitrypsin and antithrombin (AT - formerly referred to as ATIII) (57). C1 inhibitor is the most specific and most relevant inhibitor of kallikrein. It also has activity against the complement factor C1 and

factor XIIa (58). α_2-macroglobulin binds kallikrein with less specificity than C1 inhibitor but is an abundant, thus significant, plasma inhibitor. The kallikrein–macroglobulin complex retains enzymatic activity against some synthetic substrates, which makes some functional assays subject to confusion (59).

Coated Surfaces and Attenuation of Bypass-Induced Injury

Blood contact with artificial surfaces is perhaps the crucial factor in activation of the humoral inflammatory systems and cellular elements responsible for systemic organ dysfunction and coagulopathy during cardiac surgical procedures (60,61). Several components and products of normal vascular endothelium prevent platelet adherence and binding to endothelium. These include the heparins, nitric oxide, prostaglandins, thrombomodulin, prostacyclin, tissue plasminogen activator, and endonucleotidases. These are absent in the blood–air and blood–material interfaces of the CPB circuit. Two physical approaches to reduce this contact–activation have been adopted, specifically heparin coating of the exposed material and biopassivation of the blood–surface interface with surface modifications such as phosphorylcholine attachment to the circuit surface.

Coating the surface of the bypass circuit with heparin mimics the endothelial adherence of heparan sulfate, a glycosaminoglycan that binds AT and thereby inhibits thrombin adherence to the vascular wall. Heparin is bound to the foreign surface by one of several mechanisms, leaving exposed the AT-active portion, a pentasaccharide sequence. The surface-bound AT–heparin complex binds thrombin avidly. The stable AT–thrombin complex is subsequently released from the AT binding site on the surface-bound heparin, thereby allowing further circulating AT to bind to surface-bound heparin in a regenerative process (62). Heparin binding also reduces the area of foreign surface available for protein binding. As previously mentioned, fibrinogen and fibrin bind to the foreign surface and can subsequently bind and activate platelets. Heparin-coated surfaces reduce this process by reducing the thrombin-mediated conversion of fibrinogen to fibrin.

Initially, heparin was bound using quaternary ammonium salts (ionic binding) using heparin's anionic attraction to the cationic charge of the salt. The salt was then bound to the foreign surface (Fig. 38.6A). The ionic attachment of heparin to the salt is reversible and allows leaching of heparin, with the rate of leaching depending on the salt used. Alternatively, heparin may be covalently bound to the foreign surface using a linking or *spacer* molecule (Fig. 38.6B). In general, covalent binding is more stable (63). Other considerations include heparin metabolism by circulating enzymes and achieving a structural configuration that exposes the AT binding site to the circulation. Early work demonstrated the importance of the length of the spacer chain between the surface and the active heparin site (64) and the propensity of higher molecular weight heparins to activate platelets (62).

Two commercially available processes have historically been available for heparin coating. An ionically bound heparin bonded surface, Duraflo II, previously marketed by Bentley Laboratories (Irvine, Calif.) is now available only in a miniaturized CPB circuit (Ready System 200, Novosci, The Woodlands, Tex.). Porcine mucosal heparin is bound to an alkylbenzyl dimethylammonium ligand attached to an 18-carbon alkyl chain (65). This salt–heparin complex is then washed through the circuit and binds to the surface of the circuit. Alternatively, a covalently heparin-bound surface, the Carmeda Bioactive Surface (Medtronic Inc., Englewood, Colo.) is more widely available. Porcine mucosal heparin is degraded by nitrous acid and the fragments are then attached to a polyethylenimine spacer via a nitrous acid-created aldehyde group on each heparin fragment. The spacer is then bound to the foreign surface (66).

Animal and ex vivo studies have shown reduced blood trauma with heparin-coated circuits and markedly reduced requirements for heparin (67,68). Human studies have shown a reduced frequency of adherence of cellular elements to the surface, reduced blood trauma, reduced leukocyte, platelet and complement activation, and less blood loss with heparin-coated circuits (69,70). Overall, results in human studies have been encouraging but inconsistent. Comparing patients receiving conventional heparinization with and without heparin-coated bypass circuits, outcomes usually differ little (71,72). This probably reflects the relative effectiveness of adequate heparinization in attenuating bypass-induced hematological injury. Several reports have examined the efficacy of using heparin-coated circuits in the presence of low levels of heparinization. These investigations have usually shown less bleeding and transfusion and have confirmed the utility of these circuits (73,74).

Although there are case reports of patients undergoing cardiac surgery with heparin-coated circuits and no systemic anticoagulation, this practice is still highly unusual (75). The most likely utility for these devices is in long-term extracorporeal support where systemic heparinization entails increases the likelihood or severity of bleeding (76). Low dose or no systemic anticoagulation may be attempted, although reports exist of thrombus formation under these conditions (77).

A different approach to surface modification for cardiopulmonary bypass is the preparation of the circuit with a phosphorylcholine additive intended to mimic the nonthrombogenic, biopassive surface of erythrocytes and

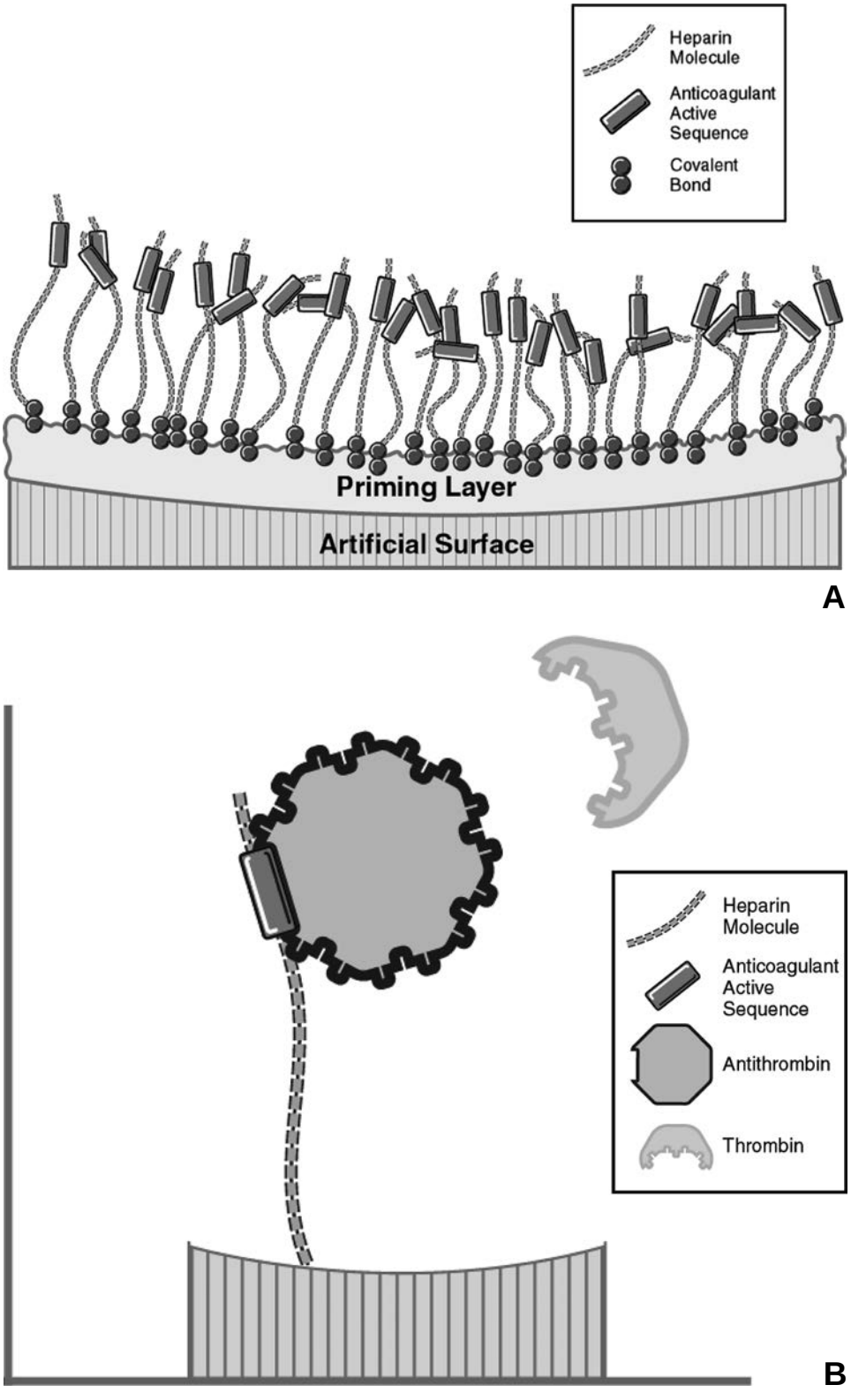

Figure 38.6 **(A)** Schematic of the Carmeda heparin coated circuit. **(B)** Interaction of bound pentacaccharide with circulating antithrombin during CPB. Schematic Medtronic Inc., Minneapolis, Minn. Carmeda is a registered trademark of Carmeda AB, Sweden.

nonactivated platelets (Physio, COBE Cardiovascular, Arvada, Colo.) (Fig. 38.7). Phosphatidyl choline residues are polymerized, and then layered onto the routine polyvinylchloride (PVC) base. PVC is hydrophobic, therefore the polymer will orient with its polar phosphorylcholine moiety stably concentrated toward the surface (78). Considerably more preclinical and clinical data exist for a biopassivated circuit, which binds fibrinogen but in a

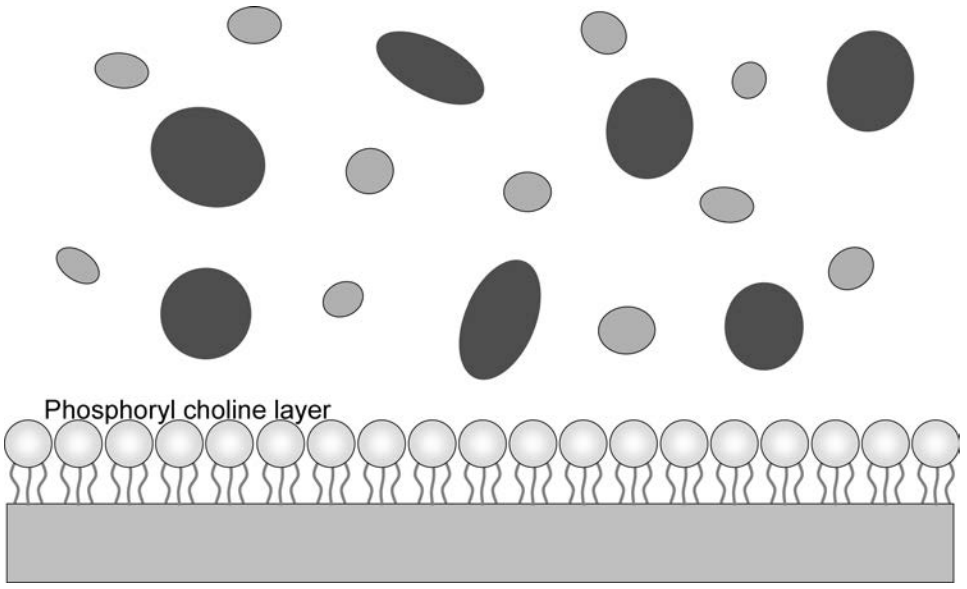

Figure 38.7 Interaction of platelets and blood cells with the Physio surface modified CPB circuit. Modified with permission from Cobe Cardiovascular, Arvada, Colo.

conformation that minimizes platelet adhesion and activation (SMARxT, COBE Cardovascular, Arvada, Colo.) (Figures 38.8a and b). Hydrophilic-hydrophobic co-polymers of polycaprolactone, when mixed with the PVC base resin during manufacture, migrate to the circuit surface and present a heterogeneous binding surface for albumin and fibrinogen. Fibrinogen domains that bind platelet glycoproteins are occupied, minimizing platelet adhesion and activation.

Studies in children and adults show increased platelet count and decreased platelet activation during cardiac operations with the use of circuits have utilize such novel surface-modifying additives (79–81). In addition, modest reductions in generation of thrombin and tissue plasminogen activator have been observed (82,83). Minimal effects have been seen on generation of complement, and the effects on bleeding and transfusion requirement have been equivocal (79–81,83).

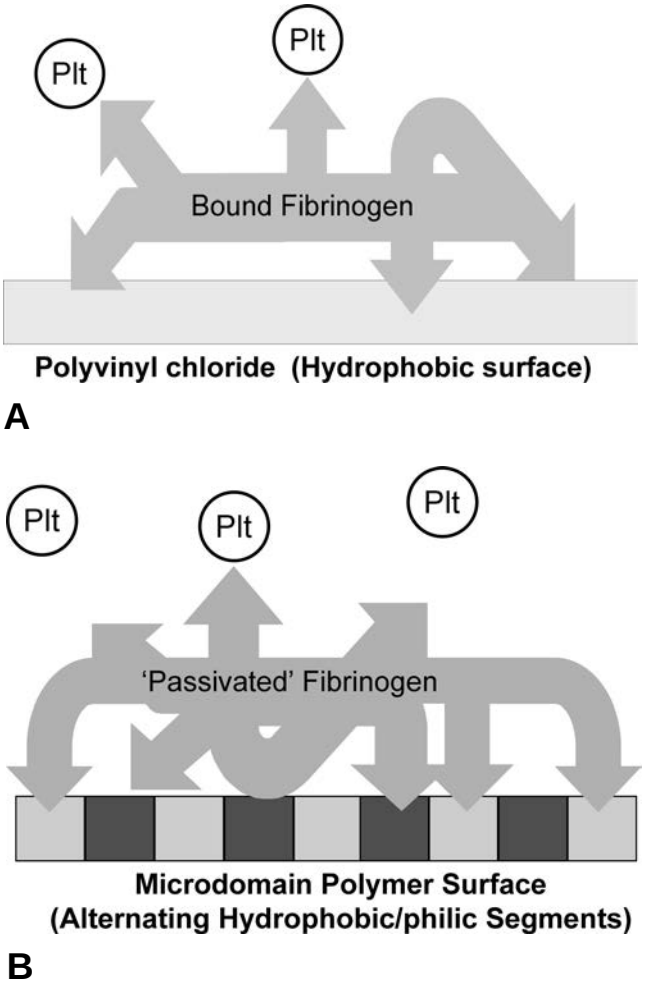

Figure 38.8 **(A)** Fibrinogen and platelet binding to an uncoated CPB circuit. **(B)** Binding to the Smar$_x$t surface modified CPB circuit. Modified with permission from Cobe Cardiovascular, Arvada, Colo.

HEPARIN

Monitoring Heparin Anticoagulation

Individual patient response to heparin is variable. Patients' blood heparin levels vary widely in response to a fixed dose, as do results of coagulation assays such as the ACT (84). Empirical heparin therapy may result in excessive, or worse, inadequate anticoagulation depending on individual sensitivity to and metabolism of heparin (85). Because of this variability, monitoring of heparin anticoagulation is extremely important.

An ideal assay establishes an anticoagulant effect that is therapeutic but not excessive. It should be sensitive at high and low ranges of response, reproducible and easy to perform. Other features of an ideal assay include: use of small amounts of whole blood, bedside availability, and reagents that are inexpensive, stable, and commercially available (86).

Assays of heparin anticoagulation can be divided into functional and quantitative assays. Functional assays, such as the TT, PT, APTT, and ACT, demonstrate the response of the individual to anticoagulation but are also affected by factors unrelated to heparin anticoagulation. Quantitative assays, such as heparin concentration monitoring, verify and quantify the presence of anticoagulant but do not document its effect (87).

The PT functional assay involves the addition of animal-derived tissue thromboplastin to recalcified, warmed, citrated plasma. PT is prolonged predominantly in response to low (less than 50%) levels of factor V, VII, or X but is relatively insensitive to heparin (88). TT measures the effect of thrombin on fibrinogen. Specifically, thrombin is added to a warmed recalcified sample of plasma from citrated blood and the time to clot formation is recorded. TT is highly sensitive to the effect of low levels of heparin on thrombin but is unclottable at high heparin concentrations. TT is affected by levels of fibrinogen and fibrin degradation products (88). APTT involves the addition of phospholipid (partial thromboplastin reagent) plus a surface activator (kaolin, celite) to recalcified, warmed, citrated plasma (88). APTT is sensitive to the effects of low dose heparin on factor Xa and thrombin, (89) but reproducibility diminishes at higher heparin doses. Like the TT, APTT is unclottable at the high heparin concentrations used during bypass (87). However, this sensitivity profile is advantageous when considering the adequacy of protamine reversal of heparin (90). APTT correlates poorly with heparin concentration and with other assays of anticoagulation such as ACT. Sources of variability in the APTT include levels of factor VIII and AT, type of activating reagent, and individual differences in response to heparin. This variability results from differences in volume of distribution, metabolism, and clearance for the drug (89).

The ACT was originally introduced in 1966 (91). In 1975, Bull et al. (85,92) suggested dosing heparin for bypass based on the response of the ACT to an initial heparin dose and continued monitoring of the ACT during bypass to predict additional heparin need. In doing so, heparin therapy was transformed from use of a collage of empirical protocols to a systematic therapy, which includes monitoring of anticoagulant effect. ACT is insensitive to low heparin levels but, unlike the TT or APTT, gives meaningful results at the high levels of heparin required for bypass. ACT uses whole blood and is quick and easy to perform at the bedside (84). Numerous problems, however, make the ACT a potentially inaccurate and imprecise assay. Individual response to heparin is variable, and the test is affected by factors unrelated to heparin. The relationship of ACT to heparin concentration is not always linear. Alterations in technique and test conditions affect precision (reproducibility). In addition, ACT endpoints are arbitrary and unrelated to clinical outcome.

ACT is a semi-automated test that has low variability in techniques and results. The Hemochron Response ACT device (International Technidyne, Edison, NJ) requires 2 mL of whole blood in a prewarmed glass tube containing celite (diatomaceous earth) or other contact activators and a magnet (Figure 38.9). The tube is placed into a rotating well within a heat block. The magnet remains dependent until the formed clot displaces it toward the center of the tube. This displacement activates a proximity switch and stops the timer (93). The ACT Plus (Medtronic, Minneapolis Minn.) device requires 0.4 mL of whole blood in a prewarmed cartridge containing kaolin. Mixing occurs by means of a plunger. As clotting blood impedes the action of the plunger, an optical detector is triggered and terminates the assay (93).

Studies comparing the performance of the Hemochron and ACT Plus devices for measuring ACT results vary somewhat, although the trend is for the Hemochron ACT to be longer than from the ACT Plus (94). This difference is accentuated when ACT is prolonged (93). The variation may result from differences in concentration or quality of contact activator, mixing technique, and technique of clot detection (94,95). The precision (reproducibility between identical samples) of the ACT varies up to 9% (84).

Other factors contributing to variability in the ACT include hypothermia, (96) severe thrombocytopenia (97) or thrombocytosis, (98) platelet activation, (99) and the antifibrinolytic, aprotinin (100). Hypothermia impairs platelet activation and the rate of the coagulation cascade. Thrombocytopenia causes a deficiency of platelet phospholipid needed for clot organization, whereas thrombocytosis and/or platelet activation neutralizes heparin via release of platelet factor-4, Aprotinin delays contact activation through its inhibition of kallikrein. Factors found not to contribute to ACT variability include age, weight, body surface area, (92) platelet count (within the normal range), and AT (97). Hemodilution has been shown in vitro to prolong ACT, (101) but other studies show no correlation between hematocrit (as a proxy for dilution) and ACT (97). Despite the claims by Bull et al. (85,102) of a linear relationship between heparin dose and ACT, most studies find ACT to correlate poorly (84,103) with heparin concentration during bypass. Lack of precision and large

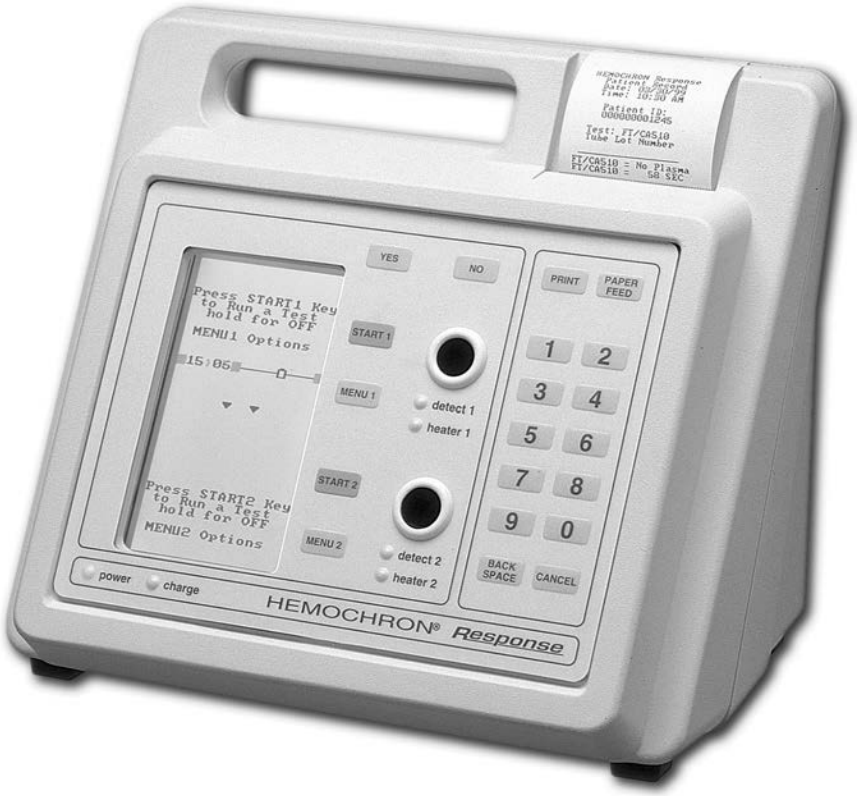

Figure 38.9 The Hemochron Response ACT Monitor. Courtesy of International Technidyne, Edison, NJ.

interpatient variability in response to heparin (up to 600%) are major factors in weakening the correlation (92).

The optimal ACT for bypass is not clear. Bull et al. (92) based their optimal range of ACT of 300 to 600 seconds on their observation that a clot could appear in the surgical field if the ACT were beneath 300 seconds and that the ACT was unreliable if over 600 seconds. Alternatively, fibrin monomer formation is inhibited at an ACT over 400, with preservation of AT, fibrinogen, and platelets (104). In addition, formation of fibrinopeptide A (a thrombin cleavage product of fibrinogen) is limited at an ACT exceeding 400 seconds (105). As such, 400 seconds is the usual target range for anticoagulation. However, the clinical benefits of this target remain unproved. Many studies show no sequelae (based on fibrin monomer formation or absence of visible clot) of an ACT as low as 250 to 300 seconds (106,107).

Quantitative assays of heparin concentration can be functional, such as the protamine titration assay, or can involve chromogenic/fluorogenic substrates for thrombin or factor Xa. The protamine titration assay is based on the principle that a clot will form earliest in the presence of an optimal neutralizing ratio of protamine to heparin. Protamine in excess of heparin will paradoxically prolong clot formation (108) as will the predictable excess of heparin to protamine. Any functional assay of heparin activity (e.g., TT, APTT, ACT) can be subjected to protamine titration (101).

The HMS Plus (Medtronic, Minneapolis, MN) is an automated hemostasis management system that uses different assay cartridges to perform several heparin monitoring functions such as a semi-quantitative whole blood heparin concentration, high range ACT and a heparin dose response assay. It consists of a cartridge with plastic wells, each containing measured reagents to which whole blood is added (Figure 38.10). The detection process uses a plunger within the cartridge. This plunger is lifted and dropped through the sample/reagent mixture. As the sample clots descent of the plunger is impeded and detected by photocells within the instrument. For estimation of the heparin dose-response, increasing concentrations of heparin are present in duplicate wells of the cartridge along with a kaolin activator and calcium. For measurement of whole blood heparin concentration, heparin in the patient's blood is titrated against increasing concentrations of protamine in the cartridge. Diluted tissue factor is used to accelerate the reaction. The cartridge channel in which the blood clots first contains the optimal ratio of heparin to protamine, approximately 10 μg protamine to1 unit of heparin. From this ratio, the heparin concentration is calculated. This technique of heparin monitoring is fast, is easy to perform, has good precision, and uses whole blood (101).

Heparin can also be quantitated with a fluorogenic assay (Protopath, Miami, Fla.). This assay uses a fluorescent

Figure 38.10 The HMS Plus ACT and Heparin Concentration Monitor. Courtesy of Medtronic, Minneapolis, Minn.

molecule (aminoisophthalic acid dimethyl ester) coupled by amide bond to a tripeptide sequence resembling the site of action of thrombin upon fibrinogen. Plasma from the patient is mixed with pooled normal plasma containing an excess of AT and a fixed amount of thrombin. Thrombin uninhibited by heparin acts on the substrate and releases the fluorescent molecule (109). This assay is quick and has a high degree of accuracy and precision. Circulating levels of fibrinogen, fibrinogen/fibrin degradation products, and AT do not affect the assay. It is sensitive to low concentrations of heparin and is more accurate than protamine titration (101,110). Drawbacks of the assay include the use of plasma rather than whole blood, the need for controls and standards for each assay, and the need for a highly skilled operator. Chromogenic assays are available and use substrates for thrombin or factor Xa activity. These assays are similar in technique to the fluorogenic assay and have similar drawbacks but have less precision (111).

Given the variability of the ACT, its imprecision, and its response to factors unrelated to heparin dose (e.g., hypothermia, platelet activation), heparin concentration monitoring is an alternative. Patients who undergo bypass with heparin concentration monitoring have significantly reduced fibrinopeptide-A formation compared with those monitored by ACT alone (111). As such, monitoring adequacy of heparin concentration may result in decreased consumption of clotting factors on bypass and improved postbypass hemostasis. Unfortunately, heparin concentration monitoring has never been shown to be superior to ACT in this regard. Heparin monitoring results in higher doses of heparin and protamine used (86,112). Impaired postbypass hemostasis may occur in these patients as a result of excess antifactor Xa activity that is not effectively neutralized by protamine (111,113). Worse yet, heparin concentration monitoring without a functional assay of anticoagulation may result in inadequate anticoagulation in the face of heparin resistance or AT deficiency (86,112).

Ultimately, the combination of heparin concentration monitoring with functional monitoring (i.e., ACT) results in optimal anticoagulation on bypass and return to normal hemostasis in the postbypass period. Protocols using these two assays in concert compared with ACT alone (predominantly in historical control subjects) result in an up to 50% reduction in protamine dose, with reduced blood loss and blood product requirement (101,108,110,114).

Heparin-Induced Thrombocytopenia

In contradistinction to the common, mild reduction in platelet count seen in patients receiving heparin (type I HIT), type II heparin-induced thrombocytopenia (type II HIT) is a less common but serious and potentially fatal complication of heparin therapy. Its incidence varies from 1% to 3% in patients receiving heparin (115). HIT is more common with bovine-origin heparin than with porcine-origin heparin for unclear reasons (116). Paradoxically, HIT is associated with thrombosis in approximately 30% to 50% of patients, with up to 30% mortality (115). The etiology is related to the presence of an IgG to heparin-platelet factor 4 complexes, which activates platelets via an Fc receptor (117,118). HIT most frequently occurs after a 4-day to 10-day latent period but will usually abate 2 to 5 days after heparin cessation. Thrombo-embolic phenomena may result from immune-mediated endothelial injury, complement activation, and platelet clumping. HIT should be strongly suspected in any patient on heparin with a precipitous drop in platelet count and or thrombosis, within days of heparin administration.

A number of assays are available to diagnose HIT, although any patient on heparin with a precipitous drop in platelet count and/or thrombosis should be strongly suspected for the syndrome. An ELISA test is available to detect the presence of serum anti heparin-PF4 IgG. This test is 99% sensitive, but only 90% specific, thus a positive result is not necessarily confirmation (118). Heparin induced platelet activation and serotonin release assays are also available to confirm the diagnosis of HIT as made by

clinical suspicion and ELISA. These assays have high sensitivity and specificity, but require washed donor platelets and are technically more difficult to perform (115,119).

Clinical management of the patient with suspected and/or confirmed HIT not undergoing CPB is relatively straightforward. All heparin should be discontinued and alternative anticoagulation should be initiated with a direct thrombin inhibitor. Ultimately, oral anticoagulation may be required. However, the management of these patients for CPB is problematic (Table 38.1). For elective CPB, it is recommended that if possible, surgery be delayed until antibodies are no longer present. HIT antibodies disappear from the circulation 50 to 100 days after discontinuation of heparin (115). Delaying surgery until antiplatelet antibodies are unmeasurable and in vitro tests show the absence of heparin-induced aggregation has been undertaken without the recurrence of HIT (120). Preoperative plasmapheresis to remove the antiplatelet IgG antibody has been described but is difficult to perform and may not be successful (121). For urgent or emergent surgery, heparin should be completely avoided, yet alternative anticoagulation strategies are limited and equally as challenging.

TABLE 38.1

ALTERNATIVES TO HEPARIN FOR ANTICOAGULATION FOR CARDIOPULMONARY BYPASS IN THE PATIENT WITH HEPARIN-INDUCED THROMBOCYTOPENIA

Surgical delay[a]
Argatroban[b]
Hirudin/Bivalirudin[c]
Prostacyclins[d]
Anti-platelet agents/GPIIbIIIa inhibitors[e]

[a] For more information see Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *Ann Thorac Surg.* 2003;76: 2121–2131 and Potzsch B, Klovekorn WP, Madlener K. Use of heparin during cardiopulmonary bypass in patients with a history of heparin-induced thrombocytopenia. *N Engl J Med.* 2000;343:515.
[b] For more information see Cleveland KW. Argatroban, a new treatment option for heparin-induced thrombocytopenia. *Crit Care Nurse.* 2003;23:61–66; Ohno H, Higashidate M, Yokosuka T. Argatroban as an alternative anticoagulant for patients with heparin allergy during coronary bypass surgery. *Heart Vessels.* 2003;18:40–42; and Lubenow N, Selleng S, Wollert HG, et al. Heparin-induced thrombocytopenia and cardiopulmonary bypass: perioperative argatroban use. *Ann Thorac Surg.* 2003;75: 577–579.
[c] For more information see Koster A, Spiess B, Chew DP, et al. Effectiveness of bivalirudin as a replacement for heparin during cardiopulmonary bypass in patients undergoing coronary artery bypass grafting. *Am J Cardiol.* 2004;93:356–359; Koster A, Fischer T, Gruendel M, et al. Management of heparin resistance during cardiopulmonary bypass: the effect of five different anticoagulation strategies on hemostatic activation. *J Cardiothorac Vasc Anesth.* 2003;17:171-175; Koster A, Loebe M, Mertzlufft F, et al. Cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia II and impaired renal function using heparin and the platelet GP IIb/IIIa inhibitor tirofiban as anticoagulant. *Ann Thorac Surg.* 2000;70:2160–2161; and Potzsch B, Madlener K, Seelig C, et al. Monitoring of r-hirudin anticoagulation during cardiopulmonary bypass—assessment of the whole blood ecarin clotting time. *Thromb Haemost.* 1997;77:920–925.
[d] For more information see Kraenzler EJ, Starr NJ, Miller ML, et al. Heparin-associated thrombocytopenia: management of patients for open heart surgery. Case reports describing the use of iloprost. *Anesthesiology.* 1988;69:964–967; Addonizio VP Jr., Fisher CA, Kappa JR, et al. Prevention of heparin-induced thrombocytopenia during open heart surgery with iloprost (ZK36374). *Surgery.* 1987;102:796–807; and Kappa JR, Fisher CA, Todd B, et al. Intraoperative management of patients with heparin-induced thrombocytopenia. *Ann Thorac Surg.* 1990;49:714–722.
[e] For more information see Smith JP, Walls JT, Muscato MS, et al. Extracorporeal circulation in a patient with heparin-induced thrombocytopenia. *Anesthesiology.* 1985;62:363–365; Koster A, Meyer O, Fischer T, et al. One-year experience with the platelet glycoprotein IIb/IIIa antagonist tirofiban and heparin during cardiopulmonary bypass in patients with heparin-induced thrombocytopenia type II. *J Thorac Cardiovasc Surg.* 2001;122:1254–1255; Makhoul RG, McCann RL, Austin EH, et al. Management of patients with heparin-associated thrombocytopenia and thrombosis requiring cardiac surgery. *Ann Thorac Surg.* 1987;43:617–621; and Kappa JR, Fisher CA, Berkowitz HD, et al. Heparin-induced platelet activation in sixteen surgical patients: diagnosis and management. *J Vasc Surg.* 1987;5:101–109.

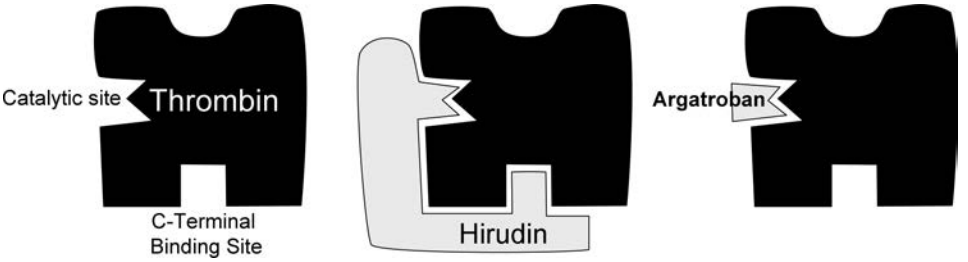

Figure 38.11 Mechanism of action of Argatroban, Hirudin and other thrombin inhibitors. (Modified with permission from Nutescu EA, Wittowsky AK. Direct thrombin inhibitors for anticoagulation. *Ann Pharmacother.* 2004;38:99–109.)

Alternatives to Heparin Anticoagulation for Cardiopulmonary Bypass

Several drugs can provide adequate anticoagulation for CPB. However, the rapid termination of heparin anticoagulation by protamine is not available for these drugs because of unavailable antagonists and prolonged metabolism. In addition, simple monitoring techniques for adequacy of anticoagulation, such as available for heparin, are usually not available for alternative drugs.

Argatroban

Argatroban is a synthetic thrombin inhibitor derived from l-arginine (Fig. 38.11). It binds directly and reversibly to the active site of thrombin, independent of AT or other cofactors. In addition, it binds to both free and clot-bound thrombin, and appears to inhibit platelet aggregation ex vivo (122). Argatroban is metabolized by hepatic cytochrome and has a half-life of 40-to 50 minutes in healthy volunteers, with termination of anticoagulant effects in 120 to 240 minutes. Hepatic, but not renal, dysfunction reduces clearance and prolongs half-life (123). The effect of Argatroban is measured well within a wide dosing range by assays of thrombin activity such as APTT and ACT. Argatroban has been safely administered to patients with HIT for hemodialysis, in percutaneous coronary interventions, in peripheral vascular surgery and CPB (122,124). In fact, it is not unreasonable to state that, with the possible exception of the patient with hepatic disease, Argatroban has become the agent of choice for anticoagulation in the patient with HIT, (125,126) although failure with Argatroban has been reported (127).

Hirudins

Hirudin is a heterogeneous polypeptide of 65 to 66 amino acids (molecular weight 7,000 Da) derived naturally from the salivary glands of the medicinal leech (*Hirudio medicinalis*). Recombinant forms of hirudin such as Lepirudin vary in form but structure but have preservation of the regions responsible for binding of thrombin, and inhibition of its catalytic site (Fig. 38.12) (128). Hirudin is a specific thrombin inhibitor, with three to five times the potency of heparin and binds to both free and clot-bound thrombin. It requires no plasma cofactor such as AT and is not affected by inhibitors such as platelet factor-4. It appears to have no effect on platelets and is nonimmunogenic. It is cleared unchanged by the kidney with first-order kinetics, after initial redistribution with a half-life of 60 to 80 minutes (129). Hirudin is also immunogenic, with a 44% incidence of antihirudin antibodies in patients receiving hirudin for anticoagulation. A review of an early safety database revealed a 0.015% incidence of anaphylaxis on first exposure and 0.16% on reexposure (130).

The effect of Hirudin is measured well at low to moderate levels by assays of thrombin activity, such as APTT and ACT (129). APTT seems to be best correlated with plasma hirudin levels and with clinical effect (131). However, at the high plasma levels required for bypass, standard clotting tests do not correlate to hirudin levels (132). Nontraditional tests such as amidolytic anti-IIa assays or thrombin-activated ACT may be required to provide meaningful data. The ecarin clotting time (ECT) has been used for monitoring hirudin anticoagulation during CPB. Ecarin converts thrombin to meizothrombin, which forms a stable complex with hirudin. Hirudin activity is inhibited while conversion of fibrinogen

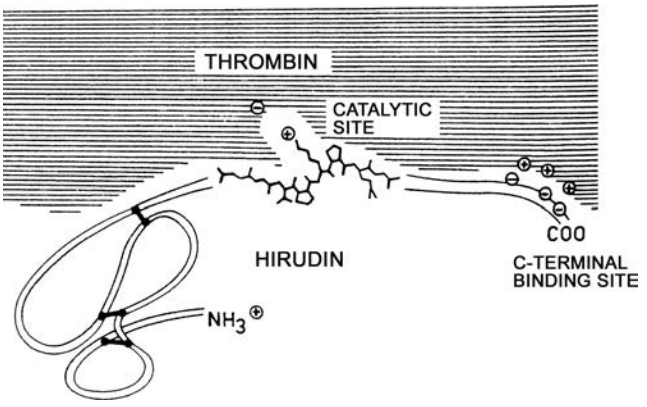

Figure 38.12 Hirudin interaction with thrombin. Secondary binding sites such as the polyanionic C-terminal region stabilize primary binding to and inhibition of the thrombin catalytic site. (Modified with permission from: Markwardt TF. Pharmacology of selective thrombin inhibitors. *Nouv Rev Fr Hematol.* 1988;30:161–165.)

to fibrin slowly occurs. ECT correlates well to plasma hirudin levels, even at high doses (133). However, ECT is adversely affected by hemodilution, and addition of exogenous plasma is required to perform the assay. A point-of-care ECT is approved by the FDA on a compassionate-use basis only at this time (TAS Analyzer, Pharmanetics, Morrisville, NC) (134).

Hirudin use has been described in angioplasty (130), in deep venous thrombosis, and in cardiac surgery. Despite its many advantages, hirudin is likely an inferior anticoagulant to heparin, which promotes inhibition of many steps in the intrinsic (contact activated) pathway. In an in vitro model of CPB, hirudin resulted in higher levels of fibrinopeptide A and prothrombin fragment F1.2 compared with heparin (135). In canine bypass models, fibrin deposition in arterial line filters was significantly increased in those dogs receiving hirudin compared with heparin. In several human studies and case reports, hirudin has been described as an effective anticoagulant for CPB, although persistent unreversible anticoagulation has been reported after CPB, especially in patients with renal insufficiency (128,136).

Bivalirudin is a small (2 kDa) synthetic thrombin inhibitor with thrombin-binding properties similar to those of hirudin (137). Unlike hirudin, bivalirudin is partially cleaved by thrombin and other plasma enzymes, changing its affinity and resulting in rapid dissociation. The half-life of bivalirudin is only 25 minutes and is less sensitive to renal dysfunction than hirudin (138). The short half-life and enzymatic route of elimination may make bivalirudin an inadequate anticoagulant for CPB (115). Because of its shorter half-life and consequent reduced postoperative bleeding, there is interest in Bivalirudin as a replacement for Argatroban (139).

Prostacyclins

Prostacyclin and its analogues have been used to inhibit platelet activation during heparin administration (140). Prostaglandins stimulate adenylate cyclase to produce cyclic AMP, an intracellular inhibitor of platelet activation and aggregation. Unfortunately, both prostaglandin E_1 and prostacyclin cause severe hypotension in clinical settings. In addition, prostacyclin is unstable at physiological pH. Iloprost is a stable prostacyclin analogue with a half-life of 15 to 30 minutes. This allows for administration by infusion with a rapid diminution of effect. Iloprost has been shown to prevent in vitro heparin-induced platelet aggregation in patients with HIT, and has been used in CPB (141,142). Blood from patients with HIT was tested perioperatively to ensure iloprost inhibition of heparin induced platelet aggregation and serotonin release (141). Iloprost was given by infusion before administration of heparin and continued until 15 minutes after protamine was given. Mild decreases in blood pressure were treated easily with infusion of phenylephrine or, rarely, norepinephrine and no abnormalities of bleeding were observed. Use of another prostacyclin analogue, epoprostenol, has also been reported in a small series of patients undergoing CPB with heparin (143).

Other drugs

Preoperative administration of antiplatelet agents has been described in patients with HIT, although not universally successfully so (144). Platelet inhibitors do not eliminate the need for heparin but may theoretically prevent the platelet activation necessary for HIT to occur. Use of aspirin and dipyridamole has been reported in two patients with known HIT. Thrombotic and hemorrhagic complications were avoided. Use of tirofiban, a short acting platelet glycoprotein IIbIIIa inhibitor, has been described in 20 patients with HIT, and shows some promise for future use (145).

Defibrinogenating agents (e.g., Ancrod) and low molecular weight heparins (LMWHs) and heparinoids, once considered imperfect but optimal choices in desperate circumstances, are now of academic and historical interest only. Ancrod, from the venom of the Malaya pit viper (*Agkistrodon rhodostoma*), (146) selectively depletes blood of fibrinogen without effect on other clotting factors or platelets. Ancrod cleaves fibrinopeptide A from the a chain of fibrinogen but, unlike thrombin, does not cleave fibrinopeptide B and does not activate factor XIII (fibrin stabilizing factor). This results in an unstable water-soluble fibrin that is rapidly acted on by the fibrinolytic system and cleared by the reticuloendothelial system. Ancrod has been used in patients with deep venous thrombosis, in major vascular surgery, and in dialysis as well as for anticoagulation in cardiac surgery, and in patients with HIT (146). Adequate defibrinogenation (target fibrinogen concentration 0.2 to 0.7 g per L) requires prolonged infusions lasting 10 to 15 hours, (147) and postbypass coagulopathy can be severe, requiring multiple transfusions of cryoprecipitate and other clotting factors.

LMWHs are small heterogeneous oligosaccharides (4 to 6.5 kDa) possessing the pentasaccharide AT-binding region found in unfractionated heparin but too small to bind AT and thrombin simultaneously, as is required for thrombin inhibition (148). Platelet interaction is also minimal (149). LMWHs are produced mainly via chemical or enzymatic digestion of unfractionated beef or pork heparin. This creates a heterogeneous array of LMWH oligosaccharides with varying bioavailability and antithrombin binding ability.

As a result, the potency and relative antifactor Xa and factor IIa activity of these products may vary considerably (150).

LMWH has been used in patients with deep venous thrombosis, (151) pulmonary embolism, (152) hemodialysis, and for those undergoing CPB (153). A major obstacle is in monitoring LMWH anticoagulant effect. Assays such as TT, APTT, and ACT respond predominantly to thrombin inhibition and are likely to be unreliable. Amidolytic antifactor Xa assays are the standard for LMWH monitoring but require advanced expertise and are impractical in a clinical setting (154). LMWH may also precipitate HIT (155).

Most significantly, LMWH is resistant to inactivation by protamine. This is most pronounced in those formulations with high ratios of antifactor Xa to antifactor IIa activity. It is likely that protamine binds most avidly to large heparin oligosaccharides but with difficulty to smaller fragments. Antifactor IIa activity is effectively reversed by protamine in milligram ratios of 1 to 1.5:1, as demonstrated by a return of TT and APTT to normal. However, antifactor Xa activity, as measured by amidolytic assay, is incompletely reversed at best (156). Increased bleeding is a commonplace accompaniment to the use of LMWH for CPB (156).

Heparin Resistance

An occasional observation is that despite administration of a usual dose of heparin before CPB, adequate anticoagulation is not achieved by laboratory estimation. Several etiologies have been offered for heparin resistance and one clinical scenario seems logical but is not fully explanatory. Some patients who have received heparin in the days before CPB fail to achieve adequate anticoagulation with usual doses of heparin (110). Although this phenomenon favors an etiology of either reduced AT levels, (157) enhanced factor VIII activity (158), or release of platelet factor 4, (159) none of these appear to be likely commonplace candidate mechanisms (160) and the cause of heparin resistance in an individual patient is usually indeterminant. Other causes of heparin resistance are low grade coagulopathic processes, severe thrombocytosis, pregnancy, and hypereosinophilia.

AT (formerly referred to as antithrombin III) is an α_2 globulin that binds irreversibly to thrombin. Heparin binds to AT to increase its thrombin-binding activity many-fold (161). In the absence of AT, heparin has no anticoagulant activity, and severe AT deficiency is associated with venous thrombosis . Administration of antithrombin concentrates (160) or fresh frozen plasma (as a source of AT) has been shown to attenuate heparin resistance, but does not necessarily implicate deficiencies of these factors as etiologic mechanisms.

PROTAMINE

Protamine, containing 67% arginine residues, is a densely positively charged substance derived from salmon sperm, although it is found in most other vertebrate species. It binds electrostatically to negatively charged heparin and effectively neutralizes anticoagulant action of heparin. However, in large doses, protamine has anticoagulant activity and antiplatelet effects. Protamine inhibits the proteolytic activity of thrombin upon fibrinogen in a dose-dependent, reversible fashion (162). Excess protamine will prolong the ACT and other measures of coagulation in human and canine models (163). This prolongation is reduced paradoxically by the presence of heparin.

Protamine reduces platelet count and impairs in vitro platelet response to agonists such as ADP, epinephrine, and thrombin (164). The mechanism for the reduction in platelet count is the electrostatic adherence of protamine to the platelet membrane. Protamine bridges platelets and causes microaggregates, resulting in decreased platelet number (165). Protamine also causes release of tissue plasminogen activator from endothelium (166).

Reversal of Heparin by Protamine

Calculation of the appropriate protamine dose at the termination of bypass presents difficulties resulting from interpatient variability in sensitivity to and metabolism of heparin. In addition, degree and duration of hypothermia on bypass affect heparin's half-life and the resultant dose of protamine required. The result of such inadequate calculation is obvious: inadequate reversal of heparin or protamine overdose.

Three strategies can be used to determine the dose of protamine needed to reverse heparin: a fixed dose regimen based on body weight or prior heparin dose, ACT titration, or determination of circulating heparin concentration and calculation of protamine requirement. Fixed, or empirical, regimens use a predetermined ratio of protamine to heparin that varies from less than 1 mg of protamine for every milligram of heparin to a 2:1 ratio. The amount of heparin to which this calculation is applied can be the initial dose of heparin or the total amount of heparin given before and during bypass (85). This technique is simple, requiring no additional equipment or operator training. However, the large variation in reversal protocols, and the inability to respond to individual variability, can result in inadequate heparin reversal or protamine overdose (92).

ACT titration uses the ACT before and during bypass to produce a heparin dose ACT dose–response curve. This curve is then used at the termination of bypass to predict

the required protamine dose (85). This technique is simple, effective, and results in an average of 50% to 70% less protamine used than in the fixed regimen (92,167). Unfortunately, ACT titration presumes a linear heparin ACT dose relationship that likely does not exist (89,97,101,110). Moreover, ACTs over 600 seconds have virtually no relationship to heparin dose (92). In addition, ACT is insensitive to low doses of heparin, so that inadequate reversal is unlikely to be detected.

Measurement of heparin concentration by protamine titration has been described for 40 years and its use has been shown to reduce protamine doses than empirical therapy for almost as long (168). Heparin concentration monitoring results in an average 30% (up to 46%) reduction in protamine dose over the ACT dose–response curve (101). Methods of protamine titration have been described above, although the most common in use is the automated HMS Plus system (Medtronic, Minneapolis, Minn.) (108). Heparin concentration monitoring results in an average 30% (up to 46%) reduction in protamine dose over the ACT dose–response curve (101).

Protamine Reactions

Hypotensive protamine reactions have been described since 1949 (169). In 1983, Lowenstein, et al. (170) described the idiosyncratic catastrophic pulmonary vasoconstriction response to protamine.

Protamine reactions have historically been classified into three categories (171): type I, transient systemic hypotension; type II, anaphylactic and anaphylactoid reactions; and type III, pulmonary vasoconstriction. Because type II anaphylactoid and type III reactions do not occur in the presence of protamine alone but require the presence of both heparin and protamine, some consider these reactions together.

Type I: Hypotension

Protamine acts like many other highly basic drugs (e.g., d-tubocurare, morphine); when injected rapidly it induces histamine displacement from basophils and mast cells, and a reduction in arterial blood pressure (172). However the drug seems well tolerated when injected slowly over 5 to 10 minutes (171). Interestingly, histamine receptor antagonists reduce but do not eliminate the response to rapid protamine infusion (173). Unlike other types of reactions where the heparin–protamine complex is required, heparin is not necessary for a type I reaction (172).

Hypotension is accompanied by reductions in filling pressure and systemic vascular resistance and appears more severe in patients with impaired myocardial contractility. A role for a direct myocardial depressant effect of protamine has been proposed, but the evidence is inconclusive in this regard. In vitro, protamine alters the contractility of isolated porcine cardiac myocytes, producing a decreased response to β-agonists and cardiac glycosides (174). This effect is also seen to a lesser extent in canine models (175). In humans, the effect is less clear. Patients with depressed ventricular function will more frequently exhibit a decrease in cardiac index than patients with good ventricular function.

Type II: Anaphylactic Reaction

Anaphylactic reactions are mediated by immunoglobulin E (IgE). Again, heparin–protamine complexes are not required for an anaphylactic type II reaction. IgE on the surface of mast cells interacts with protamine and cause mast cell degranulation (171). Clinical manifestations include all the potentially catastrophic events associated with anaphylaxis: urticaria, bronchospasm, stridor, edema, venodilation, arterial hypotension, and cardiac arrest (176).

Suspicion of allergy to protamine can be assessed in several ways including intradermal skin testing (171,176). Whole blood leukocyte histamine release is an in vitro assay of response to protamine exposure. This test has low specificity, however, and is poorly predictive of a clinical protamine reaction (177). Radio-allergosorbent testing identifies serum antiprotamine IgE (171). Protamine saturated matrix is exposed to patient serum, washed, and then developed with radiolabeled anti-IgE. This test gives a semiquantitative result but is insensitive to low quantities of IgE. This is problematic in that protamine is a relatively weak antigen and IgE levels are usually low. Moreover, a positive test does not predict a clinical protamine reaction (177).

Patients at an increased theoretical risk for anaphylactic reaction include diabetics with previous exposure to NPH or protamine-zinc insulin, patients with fish allergy, and males who have undergone vasectomy. Compared to the general population, diabetics treated with protamine-containing insulin have increased titers of antiprotamine IgG and a higher frequency (53%) of antiprotamine IgE antibodies (178). However, most reports indicate that diabetics do not have an increased rate of anaphylaxis to protamine (177). Many case reports exist of protamine reaction in diabetics, but most are not well documented as true type II-anaphylactic reactions. Moreover, these case reports must be considered in light of the relatively unreported or unknown rates of anaphylactic reaction in the nondiabetic community (171). Conceivably, these reactions could be anaphylactoid in nature, mediated by antiprotamine IgG (178,179). However several studies have shown that chronic exposure to protamine-containing insulin is a risk factor for protamine anaphylaxis with a risk ratio of 6 to 25 (178,180). However, the population

risk is low because of the low overall frequency of anaphylaxis to protamine (177,181).

Understanding of anaphylactic reactions to protamine in patients with true fish allergy (as opposed to shellfish allergy) is based almost entirely on case reports (180,182) that suffer from the same problems of reporting bias discussed above with regard to diabetics. Protamine may serve as a cross-reacting antigen in the fish allergic patient (171). In addition, individual fish allergic patients have been reported to have increased IgE, leukocyte histamine release, and positive skin testing in response to protamine (177). However, a retrospective study showed no increase in risk of anaphylactic reaction in fish allergic patients compared with the cardiac surgical population at large, (177) and the population risk is low.

Protamines are a normal component of human sperm cells. Low titers of antiprotamine IgG antibodies against these protamines develop in 22% of men within 1 year of vasectomy, (183) and can cross-react against protamines from other species (184). This cross-reactivity against protamine raised the possibility that anaphylaxis to protamine in males may be due prior vasectomy and antibody production (185). Subsequent prospective population studies have failed to prove this suspicion, (186) however this may still be a rare cause of anaphylaxis in some individuals . Prior vasectomy should not be regarded as a contraindication to protamine administration.

Type II: Anaphylactoid

Anaphylactoid reactions clinically resemble anaphylactic reactions except that IgE is not involved. In most, but not all, cases, heparin–protamine interaction is required. The heparin–protamine complex is an activator of the classical complement pathway (20). Generation of the complement fragments C3a and C5a and other vasoactive mediators result in urticaria, bronchospasm, increased capillary permeability, and hemodynamic instability. Non-heparin requiring mechanisms have also been proposed. Protamine directly activates the classical complement pathway via C-reactive protein. Complexes of protamine and antiprotamine IgG can activate complement. Protamine inhibits plasma carboxypeptidase N, the enzyme responsible for metabolism of C3a, C5a, and bradykinin (185).

Case reports of noncardiogenic pulmonary edema occurring approximately 1 hour after bypass have implicated protamine as a causative agent. This delayed adult respiratory distresslike syndrome may be a variant of the type II anaphylactoid reaction, with complement activation and subsequent vasodilation, neutrophil sequestration, and capillary leak in the pulmonary vasculature (186). However, no documentation of antiprotamine antibodies or of complement activation is presented in these reports. It remains unclear whether this is a complication of protamine or is due to other factors such as bypass-induced complement activation, endotoxin, or transfusion reaction (171).

Alternatively, this syndrome may be a result of polycation-induced lung injury. Many types of polycations, protamine included, can cause damage to the pulmonary endothelium. Mechanisms include disruption of the normal endothelial anionic charge barrier, alteration of endothelial transport proteins, or release of mediators (e.g., leukotrienes, thromboxane) by pulmonary interstitial macrophages (187). Polycation-induced lung injury clinically resembles complement-mediated noncardiogenic pulmonary edema.

Type III: Catastrophic Pulmonary Vasoconstriction

Type III protamine reactions are associated with increased pulmonary vascular resistance, decreased left atrial pressure, right ventricular failure, and systemic hypotension. Such episodes may be brief or may require reinstitution of bypass. Rechallenge may or may not result in repeated pulmonary hypertension. Heparin–protamine complexes are necessary (187,188). It is unclear whether the rate of protamine infusion affects the likelihood and severity of the reaction (189).

Animal studies strongly indicate that the type III reaction is similar to the type II anaphylactoid reaction with heparin–protamine complexes causing activation of complement (via the classical pathway), mobilization of leukocytes, and generation of oxygen-free radicals and thromboxane A2 (187). Type III reactions are not seen in animals given indomethacin or aspirin (190). Similarly, thromboxane synthetase and receptor antagonists eliminate the changes in pulmonary vascular resistance even in the presence of elevated thromboxane A_2 (191). However, complement inhibition only partially inhibits thromboxane A_2 production (192). In addition, neither leukocytes nor platelets are necessary for the reaction to occur (193, 194). The source of thromboxane A_2 appears not to be platelets, but rather pulmonary interstitial macrophages, which respond to complement activation or to heparin–protamine complexes alone to produce thromboxane A_2 and other vasoactive mediators.

The idiosyncratic nature of the type III reaction is puzzling. Clearly, some individuals and species are at higher risk for the reaction than others. For example, it is well established that certain animal models, such as sheep, goats, pigs, and dogs, are far more prone to the reaction than humans, predictably responding to heparin–protamine complexes with pulmonary hypertension (190). This difference may result from the degree of complement activation (192,195) or, alternatively, the degree of response of leukocytes, platelets, and pulmonary interstitial macrophages (171).

Alternatives to Protamine

Alternatives to protamine that have undergone preclinical and/or clinical investigation include hexadimethrine/polybrene, heparinase, and platelet factor-4. Unfortunately, none of these alternatives have shown an appropriate combination of safety and efficacy to be considered for routine use. Most often, alternatives to heparin are used for anticoagulation in the patient known to be intolerant or allergic to protamine. If heparin is used, reversal with protamine is omitted.

Hexadimethrine, also known as polybrene, is a synthetic quaternary ammonium salt with high positive charge. It effectively neutralizes heparin in a manner similar to protamine (196). Unfortunately, hexadimethrine also causes polycation-induced lung injury in a manner similar to protamine, with binding to endothelial anionic sites, an increase in capillary permeability, and a clinical picture of delayed noncardiogenic pulmonary edema (188,197). Hexadimethrine aggregates platelets via direct electrostatic interaction with resultant thrombocytopenia (165). It binds to anionic sites in the glomerular basement membrane (198) and in large doses (greater than 5 mg per kg) causes often fatal renal toxicity (199). For this reason, the drug is not available for clinical use.

Heparinase is a heparin-cleaving enzyme produced by the microorganism *Flavobacterium heparinum*. It cleaves the AT binding site of heparin, neutralizing most of its activity, but producing active LMWH fragments. Its half-life is 1 hour in vivo but can be increased to 15 hours when covalently bound to a sepharose filter. The efficacy of heparinase (defined as a return of ACT to baseline level) has been shown in vitro in heparinized human blood from bypass patients (200) and in vivo in patients undergoing cardiopulmonary bypass (201,202). However, bleeding, most likely the result of generation of LMWH fragments, appears to be a common side effect of heparinase administration and development of the drug is currently not underway.

Platelet factor-4 is a protein released from platelet α-granules with highly specific heparin neutralizing properties (203,204). It is effective against LMWH and may have more effective antifactor Xa activity than protamine (205). It can be recombinantly produced and has a half-life of about 25 minutes. In a phase I trial of patients undergoing cardiac catheterization, platelet factor-4 was found to effectively neutralize heparin without significant hemodynamic side effects (206). In a rat model, it did not affect platelet count, leukocyte count, or complement levels (205). However, in a baboon model, leukopenia and increases in the level of complement fragment C3a are seen (204). Platelet factor-4 is an endogenous protein and does not evoke immune sensitization. However, it can contribute to HIT in predisposed patients (204,205).

PREOPERATIVE ASSESSMENT

All patients undergoing cardiac surgery require a review of their hematological and coagulation status. A history of congenital and acquired hematological disease should be sought, as well as a history of renal or hepatic disease. Most patients undergoing cardiac surgery have no congenital impairment of coagulation, yet a high percentage of patients exhibit an acquired deficit. The most common causes are drug induced, notably from aspirin, heparin, coumadin, and platelet inhibitors. Preoperative alterations in fibrinolysis due to administration of streptokinase, urokinase, and tissue plasminogen activator are also commonplace. Most coagulation defects occurring perioperatively are seen at the termination of CPB. Accordingly, it is important to determine preoperatively, all possible causes of postoperative coagulopathy.

The routine preoperative laboratory investigation varies considerably between institutions. A complete blood cell count, PT and APTT are routine. A few institutions routinely order a more extensive screen, including a bleeding time, fibrinogen level, TT, a qualitative platelet function assessment, and a cryoglobulin screen, but these are not warranted unless specifically indicated (207,208). The value of the bleeding time before cardiac surgery has been extensively investigated (209,210) and has been shown to suffer from operator and local–site temperature dependence. It is a poor predictor of postoperative bleeding and its use has been condemned (208,211). The value of other preoperative tests is particularly limited, especially in predicting postoperative bleeding. The use of immediate postoperative tests is also limited, because there are poor correlations between individual tests, and even multiple tests, in predicting postoperative bleeding.

Congenital Coagulation Disorders

Hemophilia A (Factor VIII: C Deficiency)

Hemophilia A (classical hemophilia) is inherited as a sex-linked recessive gene, and in 90% of individuals, both factor VIII: C and VIII: Ag are deficient, implying reduced production. Some individuals lack factor VIII: C but have VIII: Ag. Clinically, the diseases are identical, and factor VIII: C levels parallel the severity of disease. Patients present with spontaneous and excessive bleeding and laboratory investigation reveals a prolonged APTT and normal PT, TT, and platelet count.

Before the 1960s, fresh frozen plasma was the only available therapy; however, cryoprecipitate and factor VIII concentrate have been mainstay therapy. Cryoprecipitate contains 75 to 100 units of factor VIII: C per unit, whereas

factor VIII concentrate contains 1,000 units in 30 to 100 mL. Before the early 1990s, viral transmission in concentrate pooled from multiple donors was problematic and concentrates were therefore heat-treated. Since then, recombinant forms of factor VIII concentrate have become available.

Desmopressin (DDAVP) has been shown to increase levels of factor VIII by twofold to fourfold, by causing release of endogenous factor VIII from peripheral stores (212,213). Accordingly, it is less effective as the severity of hemophilia A increases (214). Androgenic steroids have also been shown to increase factor VIII levels. Antifibrinolytics such as epsilon-aminocaproic acid and tranexamic acid have been used as adjuncts to treatment for hemophilia.

Before CPB, it is recommended that factor VIII: C levels be raised to 100% of normal, using the following formula: units of factor VIII = weight: (kg) × 40 (mL per kg) × % increase required. Because factor VIII has an 8-hour to 12-hour half-life, repeated dosing with half the loading dose every 12 hours is required. Antibodies to factor VIII: C develop in a significant proportion of patients and may make factor VIII concentrate requirements greater than usual. Accordingly, factor VIII activity must be measured preoperatively in these patients. There are many reports of patients with hemophilia A undergoing successful and uncomplicated cardiac surgery (215,216).

Hemophilia B

Hemophilia B results from a structural defect of factor IX that is inherited in a sex-linked manner. Two variants are categorized, although many structural defects are described, based on whether the PT using brain thromboplastin is normal (hemophilia B), or abnormal (hemophilia BM). Clinically, hemophilia B is indistinguishable from hemophilia A. Laboratory tests show a prolonged APTT with a normal TT and platelet count. Factor IX activity correlates with severity of the illness, although not as well as it does in hemophilia A. Unlike those with hemophilia A, those with hemophilia B rarely (1% to 5%) have inhibitors to factor IX.

Treatment is with prothrombin complex concentrations containing prothrombin and factors VII, IX, and X and factor IX concentrates (containing less than 5% of factors II, VII, and X). Because use of prothrombin complex concentrations has been associated with thromboembolic disease and disseminated intravascular coagulation, factor levels of 100% are not sought. Levels of 50% to 75% are usually adequate (217). Use of factor IX concentrates has been associated with fewer episodes of thromboembolism than occurs with prothrombin complex concentrations (218). In contrast to factor VIII dosing, factor IX requires twice the expected number of units to be given. The following formula is used: units of factor IX = weight (kg) × 80 mL/kg × % increase required. Because of the 18-hour to 24-hour half-life, only once daily dosing of half the loading dose is required (219). Individuals with Hemophilia B have successfully undergone CPB after elevation of factor IX levels (220,221).

Von Willebrand Disease

Von Willebrand disease (vWD) is a non-sex-linked trait with dominant inheritance of a deficiency of von Willebrand factor (vWF). An essential cofactor, vWF is ionically bound to factor VIII complex. This results in defective platelet adhesion and primary hemostasis at sites of vascular injury. Prevalence of the disease is approximately 1%. Unlike hemophilia, which presents with joint and soft tissue hemorrhages and normal bleeding times, vWD is associated with mucocutaneous hemorrhages and prolonged bleeding times. Subsequent laboratory testing to differentiate vWD from hemophilia includes vWF antigen level, factor VIII: C level, ristocetin-induced platelet aggregation, ristocetin cofactor activity, and multimeric analysis. Diagnosis is based on a prolonged APTT, decreased vWF: Ag level, factor VIII: C level and vWF:RCoF activity, and a prolonged bleeding time.

The disease has been classified in five subtypes, and perioperative treatment of vWF depends on the subtype of disease. The spectrum of therapies includes DDAVP, antifibrinolytics, factor VIII: C concentrates that contain vWF, cryoprecipitate, and platelets. Most patients (80%) have type I vWD and most of the remainder have type IIA. Therapy for these groups is administration of DDAVP and antifibrinolytics. Patients with type IIA also benefit from infusions of factor VIII: C concentrates containing vWF or cryoprecipitate. The rarer subtypes are not DDAVP-responsive and require blood products to replace higher molecular weight multimers (214). Individuals with vWD have successfully undergone CPB (222).

Acquired Coagulation Disorders

Cold Hemagglutinin Disease

Cold hemagglutinin disease (CHD) is mediated by several cold reactive hemaglutinating proteins. Cold reactive proteins can be seen, without apparent etiology, or in response to viral or mycoplasma infections and lymphoma. The overall incidence of observed cold reactive proteins in the general population is 0.4 to 4%, (223) with a higher incidence in males (223). Several classes of proteins are cold reactive, notably the cold agglutinins, cryoglobulins, cryofibrinogen, and Donath-Landsteiner antibodies.

Cold agglutinins are IgM autoantibodies usually directed against the red cell I antigen. Anti-I and other red-cell directed antibodies are present in low titers with low temperature reactivity in healthy individuals but are present in high titers and react at higher temperatures in CHD. After infections with organisms expressing I-like antigens, the titer of anti-I antibodies increases. Clinical diagnosis of CHD by cold provocation tests has been described (224). Coombs test, agglutinin titer, and thermal amplitude testing are usual laboratory tests (223). There is a wide range of thermal tolerance between individuals with CHD with laboratory observable hemagglutination and hemolysis occurring at temperatures between 25° and 34°C.

CPB is sometimes performed at blood temperatures as low as 25°C, and occasionally as low as 15°C. Depending on hemagglutinin titer and cold reactivity, agglutination has been observed in the CPB circuit or coronary arteries during CPB (225,226). Hemolysis in vitro and in vivo is rare because the activity of complement is temperature dependent, but has been described during cardiac surgery (227,228).

Management of CPB depends on the severity of CHD. Although plasmapheresis to reduce antibody titer has been described, management is usually by avoidance of hypothermic CPB and use of warm cardioplegia, depending on the thermal amplitude of the antibody (223,227). Where cold cardioplegia is believed to be necessary, anterograde or retrograde crystalloid cardioplegia is recommended (223). The efficacy of perioperative steroids in prevention of intraoperative CHD is unknown.

Aspirin

Aspirin is probably the most commonly prescribed antiplatelet drug in patients undergoing CPB. Aspirin irreversibly acetylates cyclooxygenases-1 and 2, inhibiting the production of thromboxane A_2 and less importantly prostaglandin I_2. Nonsteroidal anti-inflammatory drugs reversibly inhibit platelets. Because platelets have essentially no ability to generate new cyclooxygenase renewal of platelet function requires new platelet production over about a 7 day period. Aspirin inhibits the release of vitamin K dependent coagulation factors. In clinical doses, aspirin prevents activation of platelets, thereby preventing platelet aggregation and binding to platelets adherent to the damaged vessel wall. Aspirin does not inhibit nonaggregatory platelet degranulation.

Aspirin has been shown to reduce the incidence of primary myocardial infarction, the occlusion of coronary vessels and grafts after coronary artery bypass graft (CABG) surgery, or coronary angioplasty (229) and the incidence of death and stroke in patients with transient ischemic attacks. Several studies have shown increased perioperative bleeding after CABG in patients taking aspirin preoperatively (230–232). However some have observed no differences in either rate of bleeding or transfusion (232,233). Some investigators have observed an increased rate of reoperation for mediastinal bleeding, (234,235) but others have not (232,236).

DDAVP may reduce the volume of chest tube drainage after CABG in patients who recently ingested aspirin, (237) but this finding is not universal (238). The ability of aprotinin to reduce fibrinolysis and blood loss after CABG is preserved after aspirin ingestion (239,240).

Other Antiplatelet Agents

A wide variety of other drugs used commonly in the ambulatory population induce a functional defect in platelet function. These include the nitrosovasodilators, Ca^{++} channel blockers, β-blockers, α-blockers, antibiotics, and loop diuretics. These drugs impair platelet function by interfering with intraplatelet cyclic adenine nucleotides, membrane receptors, prostaglandin synthesis, and by other mechanisms.

Clopidogrel and ticlodipine selectively inhibit ADP-induced platelet aggregation. ADP is released by activated platelets to enhance further platelet aggregation, thus their administration reduces platelet aggregation at sites of injured vascular endothelium, such as with myocardial infarction. The antiaggregatory effect of clopidogrel is due to irreversible inhibition of ADP binding to P_2 purinergic receptors on the platelet surface. Antiplatelet activity begins 4 to 7 days after administration, because of a requirement for drug metabolism by hepatic cytochromes to the active metabolite. Duration is up to a week after the last dose. Because of severe and relatively frequent side effects of ticlodipine, clopidogrel is the usual drug administered. The results of large clinical trials have demonstrated an overall benefit of clopidogrel over aspirin in the prevention of vascular ischemic events (myocardial infarction, stroke, vascular death) in patients with a history of symptomatic atherosclerotic disease. However clopidogrel and aspirin seem to have a synergistic and beneficial effect in MI. In addition, Clopidogrel has better efficacy than other antiplatelet drugs, notably the glycoprotein IIbIIIa inhibitors, in prevention of death and recurrent MI (241,242). There are several series of increased bleeding, need for reoperation for bleeding, and increased transfusion in patients undergoing CPB after administration of these drugs (243,244). Because there is no specific antagonist of these drugs, treatment usually involves platelet transfusion after CPB.

Platelet aggregation can also be achieved using monoclonal antibodies (abciximab), peptide (eptifibatide), and nonpeptide (tirofiban, lamifiban, sibrafiban, xemilofiban)

antagonists of the platelet GPIIbIIIa vWF receptor. These drugs act immediately and have shorter half-lives than clopidogrel and are frequently used in emergency angioplasty and stenting. Thus, they are not infrequently still active in patients undergoing emergency CABG. All of these drugs are effective in reducing thrombosis, death and recurrent MI, but are not as clinically effective as clopidogrel in long-term trials, perhaps because of their shorter duration. There are several reports of increased bleeding during and after CABG surgery with these drugs (245,246). However the reduced severity and incidence of bleeding and shorter duration compared to clopidogrel may be advantageous and may be an indication for use of these drugs, rather than purinergic inhibitors in patients who are likely to present for emergent CABG.

BLOOD PRODUCT ADMINISTRATION: CURRENT PRACTICE AND GUIDELINES

Over 300,000 cardiac surgical procedures are performed within the United States each year. These procedures consume approximately 18% of the 22 million blood bank products transfused every year within the United States, from approximately 14 million donations (247). Accordingly, this represents a tremendous burden on an increasingly scarce resource. A recent study found that the use of allogeneic red cell transfusion for uncomplicated primary CABG surgery in a recent study remains high, at a median of two units, with considerable interinstitutional variability (248). Much of this variability in transfusion practice is not accounted for by patient factors (248,249). Both the Joint Commission on Accreditation of Healthcare Organizations and the American Association of Blood Banks require all institutions to maintain peer review of physicians' blood utilization patterns. This peer review is the responsibility of the institution's transfusion committee. Two tasks of this committee include the establishment of transfusion guidelines and the monitoring of effectiveness of these guidelines. The effectiveness of guidelines in reducing transfusion rates at individual hospitals has been well established.

The blood supply in the United States and other developed countries is the safest it has ever been (Fig. 38.13). Over the last 20 years, there have been technological advances in risk identification, low-titer viral testing, bacterial testing, leucoreduction, and pathogen inactivation that

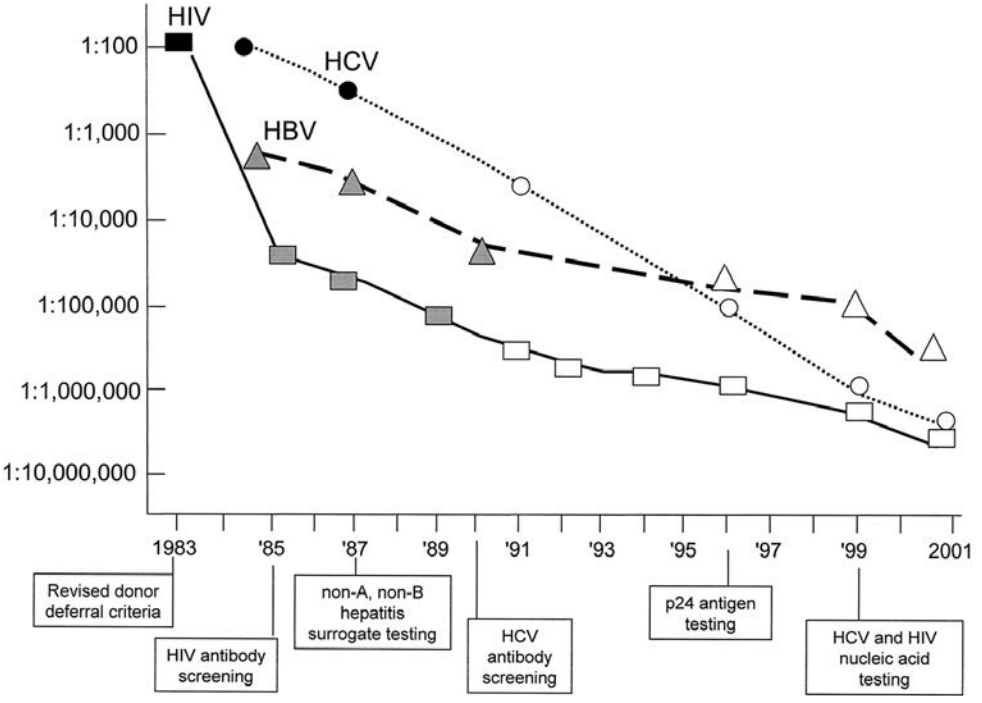

Figure 38.13 Decline in Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), and Hepatitis C (HCV) Risks of Transmission through Transfusion. Data were derived from studies sponsored by the National Heart, Lung, and Blood Institute. Estimates before 1991 are based on donor prevalence measurements (black data markers) or recipient follow-up studies (gray data markers); estimates after 1991 represent projections based on mathematical modeling (open data markers). Estimated risk of infection per unit transfused in 2000 to 2001 was 1:220,000 for HBV; 1:1,600,000 for HCV; and 1:1,800,000 for HIV. (Adapted with permission from Busch MP, Kleinman SH, Nemo GJP. *JAMA*. 2003;289:959–962.)

have significantly reduced the risk of clinically significant transfusion-transmitted bloodborne infections. Increased regulatory oversight has resulted in improved quality assurance programs in blood collection and transfusion facilities.

Blood is now so safe that risk estimates for transmission and infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) are now based on mathematical models, rather than traditional epidemiological methods (250). In 2001, these model-based estimates were per unit risks of 1:1,800,000 for HIV, 1:1,600,000 for HCV, and 1:220,000 for HBV. Nucleic acid technology (NAT) was introduced in the United States in 1998 to screen all volunteer blood donors for HCV and HIV type 1 RNA (251,252). NAT detects viral RNA earlier than the first appearance of a detectable viral or antibody markers than the currently used HCV antibody, HIV-1 antibody, and antigen assays. The current window period between viral exposure and RNA detection using NAT is approximately 11 days for HIV-1, and 8 to 10 days for HCV. Since NAT screening was implemented, the detection rate of HIV infected units is 1:260,000 units and the rate of NAT-positive seronegative HIV-viremic donations is 1:3,000,000 units. The first reports of NAT-negative transfusion of HCV-infected and HIV-infected units only occurred in 2000 and 2004, respectively (253,254). Thus, the risk of HIV viral transfusion is extremely low.

The risks of transfusion are not confined to rare viral transmission however. Additional risks include transmission of bacteria, prions, other vectors such as West Nile virus, clerical error and impairment of immune function (255,256). After cardiac surgery, impaired immune function (called allogeneic blood transfusion-associated immunomodulation (TRIM)) is arguably the most important of these, and the nearly complete implementation of routine leucodepletion reflects this concern for the overall recipient population (256,257). Although it is clear that white cell transfusion can impair immune function by several mechanisms (258–260); it is not clear what is the clinical importance of transfusion initiated immunosupression. In order to delineate the effect, many randomized clinical trials comparing allogeneic transfusion with autologous or leucodepleted transfusion have been undertaken (261–265) including for cardiac surgery (262–267). The transfusion and adverse event outcomes of these cardiac trials were contradictory, even considering the different study designs. If we postulate a dose–response relationship between transfusion volume, the effect on immunosupression and the rate of postoperative infection, we would expect to see a greater effect at high transfusion volumes (264,265).

We cannot ignore the direct fiscal costs of transfusion. In the early 1990s, the estimated cost of a single red blood cell transfusion was $150 to $500 (268). Although recent cost estimates vary, the most reliable are those from the United Kingdom for 2001, and indicate a 2.5-fold increase in transfusion costs since the early 1990s (269). When translated into U.S. dollars the per unit costs are estimated at $1,300 for red blood cells, $750 for fresh frozen plasma, $750 for platelets, and $1,700 for cryoprecipitate. The large cost increases are partly due to the introduction of leucodepletion, NAT and other measures to improve the safety of the blood supply.

There is little disagreement that reduction in needless transfusion is appropriate, cost-effective, and safe. However, there is still considerable debate on what are appropriate triggers for allogeneic transfusion, and what blood transfusion conservation measures are safe and cost-effective. The debate is fueled by inconclusive and contradictory evidence for the physiological consequences of various transfusion triggers. In contrast, institutions that undertake coordinated transfusion reduction programs are nearly always able to show a reduction in transfusion and cost savings without deleterious patient effects (270). In one institution, the introduction of new transfusion guidelines resulted in a reduction of transfusion costs by more than $1,600,000 over 3 years with a reduction of transfusion rates by 20% (270). In other multi-institutional studies, 15% of red cells, 32% of fresh frozen plasma, and 47% of platelet transfusions were deemed to be inappropriate (271).

Perioperative Bleeding

Perioperative bleeding is frequently, but not always helpfully, defined as due to inadequate surgical techniques or due to alterations in hemostasis. This distinction is usually not clear-cut, and both defects are often present concurrently. In the operating room, the distinction can be clearer. Oozing from the surgical wound, skin edges, grafts, suture lines, and catheter sites can be visualized. Postoperatively, there is a reliance on total chest tube drainage, complete blood count, and measurements of coagulation status (272). Additional tests of global coagulation and fibrinolysis can be performed. In patients in whom heparin has been reversed with protamine, coagulation can be tested using platelet count, PT, APTT, TT, and fibrinogen level. Other tests such as the Sonoclot (Sienco Inc., Wheat Ridge, Colo.), Thromboelastogram (Hemoscope Corp., Skokie, Ill.), ACT, and heparin concentration (HMS Plus, Medtronic Inc., Englewood, Colo.) can be used, but have limited ability to predict postoperative bleeding in an individual patient (273). There are over 15 point-of-care instruments claiming to measure overall, or specific, coagulation function currently available, (274) but they appear to have no greater

value than experienced clinical judgment alone, in the therapy of postoperative bleeding (275).

Antifibrinolytic Drugs

The prophylactic use of antifibrinolytic drugs during CPB has become routine in the last 10 years. Two classes of drugs are used, the lysine analogues, epsilon aminocaproic acid (EACA), and tranexamic acid (TA) that inhibit plasmin and the serine protease inhibitor, aprotinin. All three drugs have been shown to reduce bleeding and transfusion in cardiac surgery compared to placebo in sound randomized trials.

Lysine Analogue Plasmin Inhibitors

EACA and TA are synthetic analogues of the amino acid lysine and inhibit the lysine binding sites of plasmin, thereby inhibiting plasmin-induced fibrinolysis of fibrin in thrombus. Lysine analogues also stimulate the release of the endogenous inhibitor of plasmin, α_2 antiplasmin (276). Thus, the formed thrombus is not lysed during or after surgery, despite the markedly elevated plasmin levels that result from the release and action of tissue plasminogen activator during and immediately after CPB. There may be some limited effects of lysine analogues on platelet activity and by other actions, (276–278) but their importance is unknown. Although numerous dosing schedules and times have been proposed and used, these different schedules appear to have little effect on the well documented efficacy of EACA (279–282) and TA (283–286) on bleeding, transfusion, and reoperation. There appears to be little to choose between EACA and TA, as both drugs are effective, cheap, have similar pharmacokinetics and renal excretion, and have few side effects. There are no important contraindications and anaphylaxis is rare.

Serine Protease Inhibitors

Aprotinin is a previously bovine-derived, now recombinant, low molecular mass (6,512 Da) 58 amino acid polypeptide with multiple inhibitory activities (Fig. 38.14) (287). Initially derived from lung in the 1930s, it is a reversible inhibitor of the serine proteases; trypsin, plasmin, kallikrein, elastase, and thrombin, in decreasing order of sensitivity. Although aprotinin has been commercially available for many years, its use in CPB has only occurred in the last 20 years, (288) and its preparation is now as a recombinant peptide. Aprotinin is the only peptide serine protease inhibitor used for cardiac surgery. Unlike the probable single mechanism of the lysine analogues, the peptide structure of aprotinin contains several lysine residues resulting in several mechanisms of action (Fig. 38.15). Inhibition of fibrinolysis occurs via direct plasmin inhibition, like the lysine analogues, but also results from reduced tissue plasminogen activator and plasminogen, as well as increased levels of the other endogenous inhibitor of plasmin, α_1 antiplasmin (289,290).

Higher doses of aprotinin are required for inhibition of kallikrein compared to plasmin (288). Kallikrein inhibition occurs at 200 to 500 KIU per mL, whereas plasmin inhibition occurs at 75 to 125 KIU per mL (288,291). High dose aprotinin reduces kallikrein activity on bypass, reduces activation of the intrinsic pathway, and preserves AT. C1 inhibitor activity is preserved in patients receiving high dose aprotinin, (292) whereas kallikrein-C1 inhibitor complexes are reduced in vitro (21,293). Bradykinin production is reduced and high molecular weight kininogen activity is preserved (52). These findings remain in dispute, however, (294) and the clinical benefits of kallikrein inhibition, over and above plasmin inhibition are not yet clear.

An additional, seemingly unique, property of aprotinin is its serine protease activity against platelet thrombin receptors (295,296). Aprotinin can bind to the two major thrombin receptors (protease-activated receptors (PAR)) present on platelets (PAR-1 and PAR-4), preventing thrombin's action upon the thrombin receptor (Fig. 38.14). Thus, it diminishes platelet activation during CPB, while not inhibiting platelet activation by other receptors such as vWF and collagen in the post-CPB period, after reversal of heparin. This action seems to set apart aprotinin from the other plasmin inhibitors, and is probably the cause of aprotinin's greater efficacy and platelet preservation effects.

Aprotinin is effective in reducing blood loss (about 60%), reoperation for bleeding (about 50%), and transfusion (about 50%) at a wide variety of doses (297–302). Aprotinin may be associated with a reduced incidence of other inflammatory complications of cardiac surgery such as stroke, (303,304) pulmonary dysfunction, (305,306) hospital stay, and death (280). There is no evidence that aprotinin causes renal dysfunction (307). Comparing aprotinin with the other plasmin inhibitors, aprotinin more effectively reduces blood loss and transfusion in most, but not all, studies (277,308–310).

There are four issues that limit the widespread routine use of aprotinin: its cost, approximately 100 times more expensive than EACA and five times more expensive than TA; a potential for inappropriate thrombosis, especially of the injured endothelium of the coronary vein graft and during deep hypothermic circulatory arrest (DHCA); a risk of anaphylaxis, especially on reexposure; and potential difficulty with monitoring heparinization in the presence of aprotinin.

Several studies have evaluated the cost-effectiveness and cost-benefit of aprotinin administration in several patient populations (309,311). In all studies the decision point

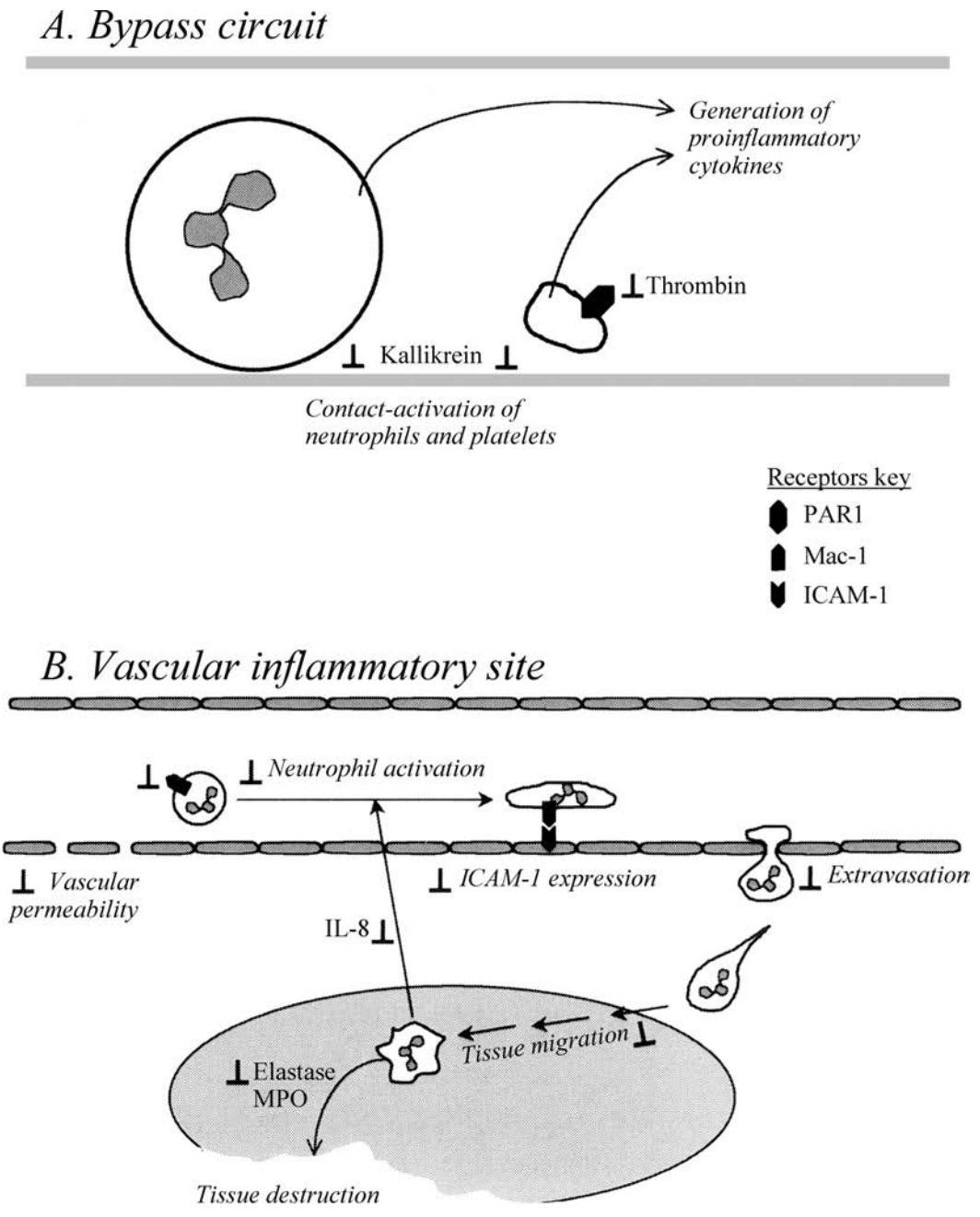

Figure 38.14 Anti-inflammatory targets of aprotinin within the bypass circuit (A) and at sites of vascular inflammation (B). This schematic summarizes the known molecular and cellular targets recognized by aprotinin in the inflammatory response to bypass. *ICAM-1* = intercellular adhesion molecule 1; PAR-1 = protease-activated receptor 1. (Adapted with permission from Landis RC, Haskard DO, Taylor KM. Title of article. *Ann Thorac Surg.* 2001;72:S1808–S1813.)

depends on the frequency and cost of transfusion and other adverse events in the specific institution and population being examined. It is likely that patients with low risk of transfusion and adverse events such as the elective CABG population will not benefit from aprotinin use, however those undergoing complex surgery with a high risk of adverse events will benefit from its use. That decision will most likely depend on institutional factors, rather than the specific cost of the drug.

Not long after the enthusiastic first reports of the efficacy of aprotinin in cardiac surgery, several reports of graft thrombosis were published (298,312–314). Subsequently, a possible but unproven explanation became apparent. Aprotinin interferes with the measurement of ACT,

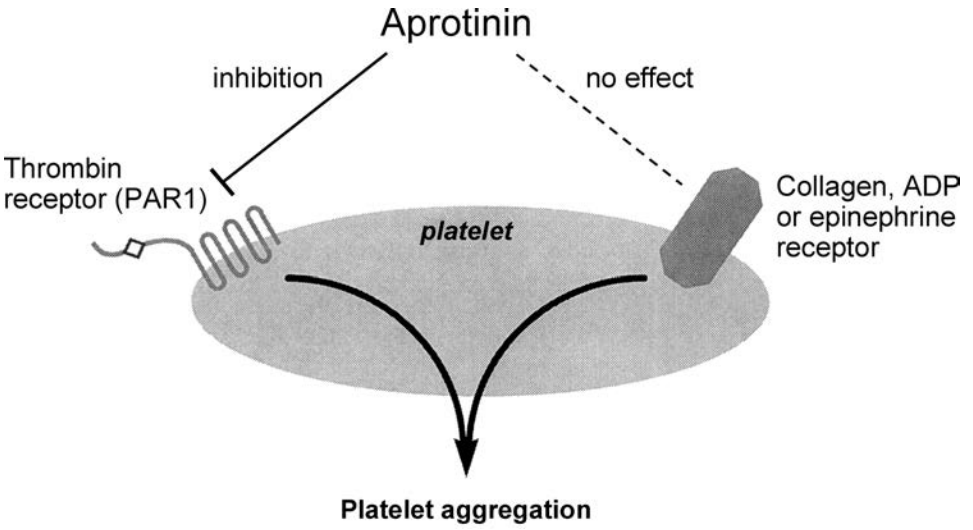

Figure 38.15 Selective blocking of protease-activated receptors 1 and 4 (PAR-1 and PAR-4)-mediated activation of platelets by aprotinin. This schematic summarizes the effect of aprotinin on platelet activation in response to proteolysis-dependent agonists (i.e., thrombin and trypsin) versus proteolysis-independent agonists (i.e., collagen, ADP or epinephrine). Aprotinin selectively blocks proteolysis-dependent modes of activation mediated via the PAR-1 and PAR-4 receptors, but not proteolysis-independent modes, which are mediated via the fibrinogen, von Willebrand factor, collagen, and purinergic receptors. (Modified with permission from Landis RC, Asimakopoulos G, Poullis M, et al. *Ann Thorac Surg.* 2001;72:2169–2175.)

(100,299,315,316) causing a prolongation of the celite-activated clotting time (CACT), but not of the kaolin-activated clotting time (KACT). Thus, target ACTs need to be increased with aprotinin use when using CACT, but not when using KACT. This is of little concern provided the effect is appreciated, but could potentially lead to inadequate heparinization and thrombosis with aprotinin, if using CACT without adjusting the target ACT. Thus, it is thought that inadequate heparinization is a potential cause for graft thrombosis. In addition, as aprotinin use is not randomly assigned, it is likely that more complex patients received aprotinin and were already at increased risk of graft thrombosis. Subsequently, studies have failed to endorse the early reports, but in one study, a subgroup showed a trend for increased vein graft occlusion (317).

The use of aprotinin during DHCA is controversial (318–324). There is obvious concern for thrombosis in the deeply hypothermic and static blood of DHCA. There are cases of adverse events occurring in this situation, (323) however other series have reported safe and beneficial effects of aprotinin (324).

Anaphylaxis to aprotinin has been reported. Independent of its source, aprotinin is a foreign peptide that can evoke an anaphylactic response (325–327). The risk of an allergic reaction to first exposure is 0.6%, but is much higher with reexposure occurring within 6 months, (326,327) and declining thereafter, in concert with loss of aprotinin-specific antibodies (328,329). Administration of a test dose may reduce the severity of any reaction, but administration within the first 6 months after initial exposure should be carefully balanced against potential advantages.

Whole Blood and Red Cell Administration: Transfusion Triggers

The hemoglobin, hematocrit, or platelet count at which red cell or platelet transfusion is administered is often referred to as the transfusion trigger (Table 38.2). The origin and modifiers of these trigger values are probably more important than any single value. That is, the factors contributing to the patient's hemoglobin level or platelet count, the patient's disease state, operative procedure, ability to compensate, and the probable clinical course should have far greater impact on management than a single numeric value. Unfortunately, the implementation of

TABLE 38.2
PUTATIVE TRANSFUSION THRESHOLDS

Hemoglobin <7.0 g/dL
Hematocrit <21%
Platelets <50-100 × 10^9/dL
INR >1.5
APTT >55 sec
Fibrinogen <200 mg/dL

transfusion guidelines places emphasis on numeric transfusion triggers. It is important to appreciate that transfusion guidelines are not indications for blood product administration; rather they are laboratory values that are usually accepted as being reasonable indications for transfusion, below which no further justification for transfusion is necessary (330).

Surgeons and anesthesiologists have a long tradition of transfusing when the patient's hemoglobin level falls below 10 g per dL, or hematocrit falls below 30%. Originating in the 1940s, this practice has persisted, seemingly unchanged. However, it is appropriate that this trigger be reevaluated. In several large series of patients with stroke, (331–333) critical illness, (334,335) and surgery in the elderly, (336,337) the safety of hemoglobin concentrations of greater than 8 g per dL has been demonstrated.

However, the lowest limit of hematocrit for an individual patient with CAD may be higher than population averages. It is known that patients routinely do well after cardiac surgery with hematocrits of greater than 23% (338–341). However, a postoperative hematocrit of less than 23% is associated with renal dysfunction, (342) but not with stroke or myocardial infarction (341). There are contradictory data regarding an optimal hematocrit after CPB (343,344). By contrast, in the nonsurgical population with CAD or heart failure, interventional and noninterventional trials have shown improved clinical outcomes with higher hematocrits (345,346).

Physiology of Acute Normovolemic Hemodilution

Normovolemic hemodilution has the potential advantages of reducing allogeneic blood transfusion requirements and improving organ blood flow. There is growing evidence that moderate hemodilution may be therapeutically useful in several disease states. In acute ischemic stroke, moderate hemodilution has been shown to improve mid-term and long-term outcomes, (347) although not all studies have observed this. Alternative explanations for this, and perhaps other advantageous organ system effects, include increased cardiac output, reduced blood viscosity, reduced exposure of platelets and white cells to endothelium, and increased washout of ischemic byproducts (348–351).

Several compensatory mechanisms occur in deliberate normovolemic hemodilution. The two primary events are reductions in oxygen-carrying capacity and viscosity. As hemoglobin concentration falls, oxygen-carrying capacity falls proportionately, yet whole-body oxygen supply remains constant, (352) or may even increase (353,354) because of increased cardiac output. With progressive hemodilution, oxygen delivery will vary species-by-species, patient-by-patient, and also depend on other pathophysiological factors such as CPB, valvular, and coronary arterial disease. Despite the reduction in oxygen delivery, the oxygen extraction can be adjusted to maintain oxygen consumption, as oxygen extraction is rarely maximized at the baseline state (Fig. 38.16) (355,356).

The compensatory increase in cardiac output occurs by three mechanisms: a decrease in blood viscosity, an increase in cardiac sympathetic stimulation, and a reduction in systemic vascular resistance, (357) primarily caused by vasodilation (358) and reduction in viscosity (359). When the oxygen-carrying capacity of blood is reduced equally by anemia or methemoglobinemia in dogs, there is a greater increase in cardiac output in anemic dogs (360). Increased cardiac sympathetic stimulation has been shown to be a further mechanism of increased cardiac output. Plasma levels of norepinephrine, but not epinephrine, are raised in euvolemic hemodilution, (359) and denervation or cardiac β-blockade reduces the compensatory cardiac output response by only a small fraction . These responses are not attenuated during long periods of hemodilution such as chronic anemia. With the increase in cardiac output, there are concomitant increases in organ blood flow, specifically in the coronary bed. The type of hemodiluting solution is relatively unimportant provided the blood volume and degree of anemia are maintained, unless the fluid is Hetastarch which significantly attenuates platelet function (361,362). Stable euvolemia is, however, more difficult to obtain with crystalloid solutions, (363) thus essentially forcing the use of albumin or other colloidal solutions.

Coronary blood flow is increased during hemodilution in individuals without coronary artery disease (CAD), (364) due to decreased myocardial vascular resistance and decreased viscosity. Oxygen extraction is maintained during moderate hemodilution, (349) and oxygen consumption is maintained or increased. With extreme hemodilution, oxygen extraction is unchanged in primates, (365) indicating the reliance on increased coronary blood flow. Epicardial predominance of blood flow in extreme hemodilution is observed, (366) indicating the relative susceptibility of the endocardium to ischemia. In patients with CAD, moderate hemodilution does not appear to be deleterious, and routine use of moderate hemodilution after CPB appears to be safe (367). In addition to compensatory reserves of myocardial oxygen consumption, there are significant reserves in myocardial mechanical function. Accordingly, the impairment in mechanical function in ischemic areas of the heart can be compensated for by myocardium that has normal contractility and perfusion (355,360). Importantly, the hospital

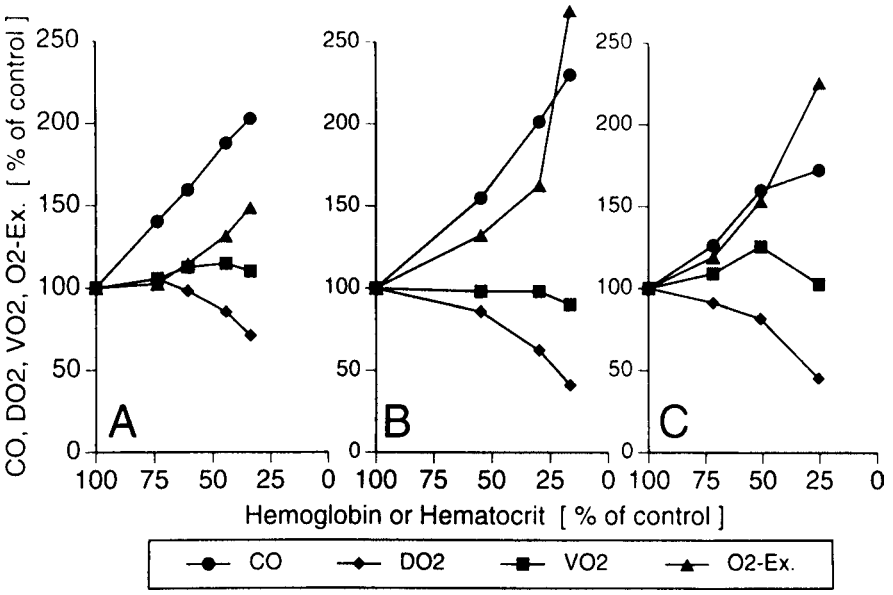

Figure 38.16 Relative changes in cardiac output (CO), oxygen delivery (DO_2), oxygen consumption (VO_2), and oxygen extraction (O_2 Ex.) during progressive hemodilution: **(A)** in pigs (redrawn by permission according to van Woerkens E, Trouwborst A, Duncker D, et al. Catecholamines and regional hemodynamics during isovolemic hemodilution in anesthetized pigs. *J Appl Physiol.* 1992;72:760–769); **(B)** in baboons (redrawn by permission according to Moss G, DeWoskin R, Rosen A, et al. Transport of oxygen and carbon dioxide by hemoglobin-saline solution in the red-cell free primate. *Surg Gynecol Obstet.* 1976;142:357–362); **(C)** in dogs (redrawn by permission according to Messmer K, Sunder-Plassmann L, Klovenkorn W, et al. Circulatory significance of hemodilution: rheological changes and limitations. Adv Microcirc 1972;4:1–77). Note that during initial hemodilution, the increase in cardiac output is the most important compensatory mechanism to maintain oxygen delivery at prehemodilution values. In more advanced hemodilution stages, the increase in cardiac output cannot fully compensate for the decrease in arterial oxygen-carrying capacity any more and oxygen delivery decreases. Oxygen consumption is then maintained via an increase in oxygen extraction. Redistribution in favor of heart and brain is observed only during extreme hemodilution. (Reprinted with permission from Spahn D, Leone B, Raves J, et al. Cardiovascular and coronary physiology of acute isovolemic hemodilution: a review of non-oxygen carrying and oxygen-carrying solutions. *Anesth Analg.* 1994;78:1000–1021.)

course and postoperative exercise tolerance were not different between patients transfused to hematocrits of 32% and those transfused to hematocrits of 25%.

There is no evidence on the safety of normovolemic hemodilution in β-blocked patients with CAD. The normal compensatory increase in cardiac output is diminished by β-blockade in animals. Yet the additional workload, and therefore oxygen demand, is also decreased. A "safe" hematocrit level probably depends on the extent of stenotic CAD, ventricular function and reserve, myocardial workload, and other as yet undetermined factors. It would be unwise to state a single safe hematocrit for patients with CAD. It is likely that a hemoglobin concentration of at least 7.5 g per dL is not a cause of ischemia or impaired contractile function in most patients with CAD. However, low hematocrits may be associated with postoperative renal dysfunction and other adverse outcomes (342,368).

Platelet Administration

Thrombocytopenia is routinely associated with CPB. Hemodilution accounts for a significant proportion of this process; sequestration, adhesion, and destruction within the CPB pump oxygenator and tubing account for the remainder (369). There is considerable controversy regarding platelet transfusion. In the patient with excessive bleeding after CPB, there are usually coexisting etiologies: thrombocytopenia, factor deficiency, fibrinolysis, and activation of inflammatory processes. Treatment of excessive bleeding necessitates an algorithmic approach of which platelet transfusion is only one methodology.

The CPB-induced reduction in platelet count depends on patient blood volumes and pump prime volume; a reduction of platelet count of approximately 30% is usual. Within minutes after the initiation of CPB, there is a further

reduction in platelet count. Sequestration of platelets (usually intrahepatic) as a consequence of hypothermia accounts for some of this thrombocytopenia. Platelet adhesion to the foreign surface of the pump and oxygenator undoubtedly accounts for a significant proportion. Platelets adhere to fibrinogen and other proteins that are bound to the tubing. Activation and aggregation are inevitable consequences of adhesion. An often overlooked etiology of thrombocytopenia is activation and destruction by surgical suction. Additionally, platelets aggregate and are activated by protamine and heparin–protamine complexes. Platelet counts usually rise by about 50% over the first 2 days after CPB and are normal within 1 week. The delayed return to normal probably reflects the ongoing inflammatory and procoagulant response to CPB.

Not only is platelet number reduced by CPB, but platelet function is also reduced. Less qualitative emphasis has been placed on this aspect because it is more difficult to measure. Although we can confidently say that CPB induces a platelet function deficit and that this deficit is due to platelet aggregation and activation, the exact mechanisms of this process are less clear. Hypothermia is a causal etiology. Factors associated with impaired platelet function are duration of CPB, type of CPB apparatus, volume of surgical suction, degree of hypothermia, heparin, protamine, and endogenous circulation platelet inhibitors.

Clinical practice with regard to platelet transfusion rates varies considerably between institutions and cannot be accounted for by patient factors (248). Part, but not all, of the explanation for the variability is due to inability to qualify the platelet contribution to bleeding. Platelet count, by automated counters, may be artificially high due to red cell and platelet fragments being counted as platelets. Platelet function is difficult to measure in the clinical environment. An estimate of platelet function can be obtained by thromboelastography, Sonoclot, and other semi-automated methods. All of these methodologies are time-consuming and sporadically used. Systematic laboratory approaches in concert with systematic clinical protocols are the best implementation of this technology. Because of the time required to obtain results and subsequently obtain blood products, it is necessary to obtain heparinized blood while on bypass. One approach is to use heparinase to obtain a coagulable sample.

The use of platelet count as a transfusion trigger for prophylactic platelet administration is to be condemned. There is no evidence of clinical benefit from prophylactic platelet transfusion except perhaps for emergency surgery after recent use of a specific platelet inhibitor, excluding aspirin (244,370,371). There is, however, an obvious place for platelet transfusion in the bleeding thrombocytopenic patient. Both the extent of bleeding and level of thrombocytopenia that indicate platelet transfusion are open to debate and clinical interpretation. Many different arbitrary volumes of chest tube drainage and platelet counts have been proposed as being triggers for platelet transfusion.

Platelets are available in single donor platelet pheresis or multiple donor pooled platelet products. Single donor platelets have the advantages of reduced possibility of infection and alloimmunization but are more expensive and difficult to harvest. Between five and eight single platelet pack equivalents are contained in a single donor pheresis pack. Pooled platelet bags contain platelets from five to eight donors, with greater than 55×10^9 platelets per donor in 50 to 75 mL of plasma. Once pooled, platelets should be transfused within 6 hours. Platelets can be transfused without regard to ABO or Rh grouping under most circumstances.

Coagulation Factor Administration

Plasma products, obtained from the fractionation of donor whole blood, have undergone a meteoric rise in use over the last 20 years. Like all other blood products, their use is variable across institutions, unexplained by patient parameters. The largest use of blood products during surgery is seen with CABG surgery.

Fresh frozen plasma is separated from whole blood and frozen within 6 hours of collection at -18°C. Some loss of the labile factors V and VIII occurs (approximately 50%), but the remaining factors are close to 100% preserved. Because only 25% to 40% of normal circulating factor levels are required for normal hemostasis, most coagulation factor deficiencies are corrected by transfusion of four units of fresh frozen plasma. Larger requirements will be seen in ongoing losses and fibrinolysis.

It is highly likely that a significant proportion of fresh frozen plasma transfusions in cardiac surgery are unnecessary and do not contribute to preventing postoperative bleeding, especially those for prophylactic indications. Although six small studies have examined the routine use of fresh frozen plasma after cardiac surgery (372,373), a meta-analysis of those studies has shown no beneficial effects from its routine use (374).

Blood Conservation Techniques for CPB

In the early days of CPB technology, the need for large pump-priming volumes and extensive pump-induced destruction of the formed elements of blood resulted in large allogeneic blood requirements. Fresh whole blood was a routine requirement and use of platelets and fresh frozen plasma was almost routine. Technological advances

in CPB materials and methods have largely reduced this transfusion requirement, however, practitioners have also learned to appreciate the safety of hemodilution.

Because of the financial and social cost of allogeneic transfusion and the limited blood supply, it is incumbent upon the physician to use appropriate opportunities to reduce the use of allogeneic blood products. Several techniques are used for prevention of transfusion during cardiac surgery (Table 38.3). The need for blood conservation is still crucial given the increasing demand for blood products and the still residual possibility of viral and bacterial transmission, isoimmunization, incidence of wound and other infections, and graft-versus-host reactions. However, the practice of cardiac surgery has changed, with a greater percentage of patients undergoing nonelective surgery, thus precluding preadmission autologous blood conservation techniques.

Autologous Red Cell Donation

Preoperative autologous donation represents a theoretically ideal mechanism of blood conservation. Unfortunately, it is perceived to be feasible only in a relatively small subgroup of patients, because of short waiting times and other factors that are perceived to prevent donation (375) and its cost-effectiveness has been questioned (376). Some reasons for this failure are because patients do not always have the requisite 1 to 3 weeks available to them before their surgery, come from distant locations, are anemic, or are correctly or incorrectly perceived to be too unstable to donate blood. In addition, the costs of autologous blood donation are higher than those for allogeneic blood transfusion (377). Several large studies have investigated the use of autologous predonation, (378–380) and several have shown the efficacy of collection and transfusion of an average of three units of autologous blood (378,381). Collections of less than three units have conventionally been less efficacious because the rate of allogeneic transfusion in this group has been high. Transfusion of three or more units of autologous blood has been associated with reduced rates of allogeneic transfusion and higher discharge hematocrits. Obviously, this group is a low risk group, often larger nonanemic males who are undergoing elective surgery and thus are likely to have good long-term results, independent of autologous predonation.

Predonation of autologous blood has been shown to reduce preoperative hemoglobin by approximately 2 g per dL when an average of two units are harvested over 2 to 3 weeks (382). Donation is rarely associated with morbidity, usually minor, and overall appears to be well tolerated even in relatively sick patients. A proportion of patients require operation during the harvest period. This fraction does not appear to be higher than the natural course of disease although this is open to debate (383).

Because of concerns over the time taken to achieve an adequate harvest of autologous blood, erythropoietin has been used to increase red cell mass for harvest. Administration of erythropoietin with or without concurrent iron administration enables greater harvest of red cells before surgery (384,385). Erythropoietin has also been shown to improve hematocrit in anemic patients before CABG surgery. It may also have a role in improvements in cell-mediated immunity after CPB. Its physiology and efficacy have been recently reviewed (386).

Autologous Platelet Donation

The most common clinical use for plasmapheresis is to remove pathogenic antibodies. Examples of this use are HT with thrombosis, cold agglutinin disease, and hyperviscosity syndrome. A few undergo preoperative harvest of platelet rich plasma (PRP), which must be performed in the 24 to 72 hours before surgery or during surgery because of the relatively short half-life of stored platelets (5 days). Practically, because of shorter preoperative admissions, PRP collection is usually performed in the operating room, before CPB. Patients with preexisting thrombocytopenia, coagulation disorders, and hemodynamic instability, but

TABLE 38.3

AVAILABLE MEANS OF REDUCING ALLOGENEIC BLOOD TRANSFUSION DURING AND AFTER CARDIAC SURGERY

Preoperative

Autologous predonation of whole blood, red blood cells, FFP, platelets
Pheresis of platelets and FFP
Erythropoietin

Intraoperative

Institutional program of guidelines for allogeneic blood product administration
Rigorous surgical technique
Pre-CPB normovolemic hemodilution
Pheresis of FFP and platelets
Nonsanguinous prime
Whole blood collection at CPB onset
Retransfusion of pump blood
Cell saver or ultrafiltration of pump blood
Drug therapy
Antifibrinolytic agents
DDAVP

Postoperative

Institutional program of guidelines for allogeneic blood product administration
Shed mediastinal blood transfusion

FFP, fresh-frozen plasma.

not those with moderately low left ventricular ejection fractions, are usually excluded. The volume of platelets obtained by this method is between 9% and 30% of the circulating platelet pool (387,388). Unfortunately, this may frequently be an inadequate number of platelets to be effective in reduction of blood loss after surgery. An effective platelet pheresis product requires 3×10^{11} platelets, (389) yet this is frequently not achieved with smaller volumes of platelet pheresis (388). The failure or inability to withdraw adequate numbers of platelets probably represents the single greatest obstacle to the efficacy of platelet pheresis. The use of one to two blood volumes of pheresis does not produce the number of platelets needed for treatment of a severe bleeding diathesis. Accordingly, when most needed, platelet pheresis is ineffective, but it is most commonly used when there is little bleeding or coagulopathy, a situation that rarely requires platelet transfusion. Technical advances may improve the harvest of platelets (390). The use of intraoperative autologous PRP transfusion has been associated with, (387,391,392) and without a reduction in transfusion requirement (393–395). Most of these studies are flawed by difficulties with blinding and failure to define transfusion triggers. Nevertheless, most studies have found an effect of platelet pheresis. The two largest studies of PRP, (392,396) totaling 577 patients receiving PRP, found reductions in blood loss and allogeneic red cell replacement.

Efficacy of Acute Normovolemic Hemodilution

Deliberate acute normovolemic hemodilution (ANH) entails the simultaneous removal of whole blood from the patient and transfusion of crystalloid or colloid volume replacement before CPB. ANH has been both associated with, (397–399) and without (400–402) decreases in allogeneic transfusion requirement. The safety of ANH is well established, but its efficacy is open to debate (403,404). The rationale for this debate revolves around the volume of red cells (and platelets) that can be safely harvested in the immediate prebypass period. Two techniques are used. The most common is the removal of blood from the central or arterial line into citrated bags before heparinization. It is rare with this technique to be able to harvest more than 1,000 mL of blood given the time constraint. The second technique is the removal of blood from the venous line to the pump, after heparinization, at the onset of bypass. Similarly, it is rare to be able to withdraw more than 1,000 mL of blood. Thus, the effectiveness of ANH is limited by the amount of blood that can be withdrawn. Removal and transfusion of 1,000 mL of blood rarely improves platelet count or function by a clinically significant amount, because the number of retransfused platelets is low compared with the circulating platelet pool. The number of red cells is less important because red cells are consumed less than platelets during bypass. Accordingly, their number and function are little affected by ANH, provided the contents of the oxygenator and all suctioned blood are transfused at the end of CPB.

Cell Savers and Ultrafiltration of Pump Blood

Three methods of administration of the remaining pump blood volume at the end of CPB are possible. These are centrifugation using a cell saver, ultrafiltration using a hollow fiber ultrafilter, and retransfusion of unprocessed blood. The latter two techniques have the advantage of retaining platelets, plasma proteins, and coagulation factors but the infusate is heparinized, therefore requiring additional protamine for reversal (405). In addition, ultrafiltration exposes the infusate to high transmembrane pressures that can potentially worsen hemolysis. Cell-saver technology produces a red cell-only infusate with negligible circulating heparin, platelet plasma protein, or coagulation factor levels. Comparing the use of cell savers with ultrafiltration upon discarded surgical suction and the remainder of the CPB pump volume, the ultrafiltered blood is a more red-cell concentrated and less platelet and coagulation factor-depleted product than the cell-saver blood (406). Infusion of centrifuged blood has been associated with longer PT, APTT, and TT than direct infusion or ultrafiltration; infusion of ultrafiltered blood is associated with higher fibrinogen levels and colloid oncotic pressures (407). These changes do not persist beyond 6 hours. Some studies have been unable to differentiate between the coagulation states after infusion of ultrafiltered and cell-saved infusate (408).

Shed Mediastinal Blood Transfusion

In 1978, Schaff et al. (409) reported a 50% reduction in allogeneic red cell transfusion requirement with transfusion of the shed mediastinal (SMB) blood from chest drainage tubes. The same authors and others have demonstrated the efficacy of SMB transfusion after CABG surgery in reducing allogeneic red blood cell transfusion (410–413). The majority of studies of SMB are profoundly flawed by low sample size, historical controls or the absence of randomization, blinding, transfusion triggers, and transfusion protocols. The safety and efficacy of SMB is debatable (414,415). The majority of larger randomized studies have failed to demonstrate a significant reduction in red blood cell transfusion (416–419). In addition, several studies showed that SMB transfusion had the surprising effect of reducing allogeneic red cell transfusion, greater than the volume of red cells transfused in the SMB transfusion. Complicating several studies has been the stated or implied

rationale for the study, being a justification for a change in institutional practice or the introduction of SMB to the institution. Additionally, it is also difficult to blind investigators and providers to the use of SMB.

Transfusion of SMB has been shown to adversely affect measurements of coagulation, both with, (420) and without, (409,421,422) an increase in postoperative bleeding. SMB is a defibrinogenated thrombocytopenic admixture that does not usually clot in the collection system. Several studies have examined the composition of SMB. The hematocrit of SMB is approximately 20% but varies considerably, depending on the rate of active bleeding, time after surgery, and volume of surgical wash remaining in the pleural cavity and pericardium at the end of surgery (423). Additionally, considerable red cell hemolysis occurs. Plasma hemoglobin levels of 4g per L in the infusate are common (424). However, transfusion of SMB has not been associated with hemoglobin-induced renal failure, (425,426) most likely because the total free hemoglobin load is low (approximately 3 g for an infusate of 700 mL).

Fibrinolytic products and tissue factor (a profound activator of the extrinsic pathway of coagulation) are seen in SMB and in circulating blood after autotransfusion (427,428). It is unlikely that routine volumes of SMB transfusion can overwhelm the body's mechanisms for "mopping up" products of fibrinolysis. Studies, with few exceptions, have not been able to demonstrate increased bleeding in patients who received SMB transfusion. Only one group has shown an increased chest tube drainage, (420,429) and no study has demonstrated an increased rate of reoperation for bleeding (423,430).

Some studies have demonstrated bacterial contamination of SMB, predominantly by diphtheroids and coagulase-negative staphylococci, albeit without clinical evidence of sepsis, (419,431) but one study has shown an increased incidence of infection after SMB transfusion (426). Cardiac enzymes, notably creatine kinase and lactate dehydrogenase, are also elevated in SMB fluid. Transfusion of SMB elevates circulating creatine kinase and lactate dehydrogenase levels (432,433). Some have argued that SMB should not be transfused because it may confuse the diagnosis of myocardial infarction. This is rarely of importance, and avoidance of potential difficulty in a laboratory diagnosis alone is not adequate justification for avoidance of SMB transfusion. Overall, there is little support for routine use of SMB transfusion.

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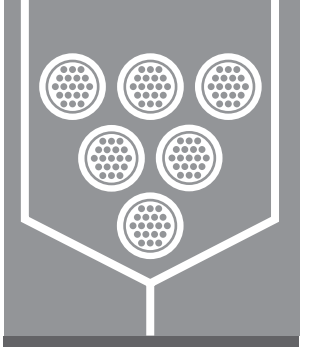

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Blood Loss and Transfusion Alternatives in Vascular Surgery

Richard K. Spence

The specialty of vascular surgery has changed drastically in the last 10 years as surgeons have embraced minimally invasive procedures and endovascular approaches to blood vessels. Renewed recognition of the risks and inherent dangers of allogeneic blood that spurred the movement toward bloodless surgery and the search for alternatives to allogeneic blood has extended into vascular surgery (1). Where traditional open procedures remain, more attention is now paid to minimizing blood loss, avoiding transfusion, and the more judicious use of allogeneic blood products. Alternatives in use range from return of shed blood with cell salvage to control of diffuse capillary bleeding with fibrin glues. Increased knowledge of the coagulation/fibrinolytic system has lead to the development of drugs that can control or might exacerbate bleeding. As a result, the appropriate use of blood and blood product transfusion remains a topic of interest to the vascular surgeon. This chapter will review aspects of anemia and bleeding and the role of transfusion in vascular surgery.

BLOOD LOSS, TRANSFUSION, AND OUTCOMES IN VASCULAR SURGERY

Both blood loss and transfusion are significant independent predictors of adverse outcomes in vascular surgery. Bui et al. (2) found blood loss to be among significant intraoperative predictors of perioperative cardiac events in 59 patients who had thoracic aortic grafting. Asensio et al. (3) reported a mortality rate from exsanguination of 82% in 148 patients with iliac artery injuries. Intraoperative blood loss greater than 500 mL was a significant, univariate predictor (P=.0006) of increased length of stay in 240 patients who underwent open abdominal aortic surgery at Pennsylvania Hospital between 1994 and 2000 (4). Bastouinis et al. (5) reported a similar association between the amount of blood transfused and postoperative admission to the intensive care unit. Postoperative renal failure and transfusion requirement were independent correlates of mortality in 334 patients with thoracic aortic aneurysms treated with the clamp-and-sew approach (6). An interesting study of postoperative delirium in vascular surgical patients demonstrated an association between this entity and blood transfusion (7). Haynes et al. (8) measured inflammatory mediators in transfused and nontransfused patients after aortic surgery. Neutrophil elastase (p = 0.008) and TNF-alpha (p = 0.015) were both significantly increased in transfused patients and transfusion was associated with increased mortality. This knowledge that the amount of blood loss and the need for transfusion worsen outcomes should prompt vascular surgeons to examine their practices with the goal of decreasing blood loss and minimizing transfusion.

Bleeding in the Vascular Surgery Patient

Although blood and vascular surgery go together, it does not follow that blood *loss* and vascular surgery should or must. Vascular surgeons routinely clamp, cut, and repair the major blood vessels that other surgeons meticulously

avoid when resecting or revising adjacent structures. Because of the nature of the operations vascular surgeons perform, it is essential that the he or she understand ways to avoid or minimize bleeding. This section will review some approaches to this problem in both the elective and emergency vascular surgical patient.

Preoperative Aspects

A careful preoperative evaluation of patients is essential if blood loss is to be reduced and appropriate plans for transfusion alternatives are to be made. The preoperative measurement of the hemoglobin level and hematocrit (H&H) will detect the presence of any anemia, which can be investigated further with red cell indices. Because anemia increases the risk of transfusion in surgical patients, it should be identified early and corrected before surgery if at all possible. A number of strategies for normalizing H&H before surgery are described elsewhere in this text.

Many vascular surgeons measure the prothrombin (PT) and partial thromboplastin times (PTT) in all patients who are to receive heparin anticoagulation. Some reserve these tests for those who are to undergo major-vessel surgery, i.e., aortic. A preferable approach is to question each patient about his or her bleeding history, since most significant bleeding problems are congenital and have been present since childhood, or are related to specific medications and disease processes. Coagulation studies should be reserved for patients with clinical indications, e.g., a history of liver disease, malignancy, renal failure or anticoagulant therapy (9,10). Similarly, routine platelet measurements are of little value, since deficiencies caused by abnormal production or increased destruction will be detected primarily by a good history and physical exam and since qualitative defects will not be reflected in abnormally low counts (11,12).

A variety of drugs inhibit platelet function, either by design or as a side effect. Mechanisms by which such drugs might act include: blocking cyclooxygenase or thromboxane synthetase, blocking the thromboxane A2 receptor, increasing intraplatelet cAMP or GMP, or by directly blocking platelet receptor GpIIb/IIIa. Aspirin irreversibly inhibits cyclooxygenase, thus blocking platelet conversion of arachidonic acid to thromboxane A_2. The aspirin effect lasts for the life span of the platelet. Because thromboxane A_2, PGG_2, and PGH_2 are important stimulants for platelet aggregation, formation of the initial hemostatic plug is impaired. The bleeding time is prolonged, and platelet aggregation studies demonstrate a consistent abnormality. Other nonsteroidal anti-inflammatory agents show similar but less pronounced effects. Because cyclooxygenase is also responsible for the production of PGI_2 by endothelial cells, the release of this substance is altered as well.

GP IIb/IIIa inhibitors inactivate platelets for variable periods of time depending on the pharmacodynaimcs of the specific drug. They inhibit binding of fibrinogen and other adhesive ligands to platelet GP IIb/IIIa receptors on the surface, thereby preventing the release of more platelet activators, platelet activation, platelet aggregation, and thrombus formation. Eptifibatide and tirofiban are small molecules that incorporate into the amino acid sequence binding pocket of the GP IIb/IIIa receptor. Abciximab is too large to fit into this sequence and therefore acts like a cap or umbrella, covering the receptor. Eptifibatide and tirofiban have concentration-dependent antiplatelet effects, achieving full activity when the molecules of drug to GP receptors is $>$100:1. Abciximab has full activity with 1.5 molecules of drug to 1 receptor. Peak antiplatelet response is seen within 1 hour of giving Eptifibatide. Bleeding times decrease within 15 to 30 minutes of drug discontinuation, with recovery of platelet function within 4 hours of drug discontinuation in vitro (2 to 4 hours in healthy subjects). Within 5 minutes, 72% to 96% of platelet aggregation is inhibited after initiation of Tirofiban therapy. Platelet aggregation returns to pretreatment levels 4 to 8 hours after drug discontinuation. Abciximab produces inhibition of $\geq$ 90% of platelet aggregation within 2 hours of drug initiation. Platelet function generally recovers approximately 48 hours after drug discontinuation, although Abciximab remains in systemic circulation for 15 days or more in the platelet-bound state. Aciximab in particular is resistant to platelet infusion since the drug redistributes and binds to transfused platelets, rendering them inactive. All patients should be asked about the use of warfarin-based anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs, and platelet inhibitors since all of these can lead to increased bleeding. When feasible, these agents should be stopped well in advance of any planned surgery that carries a high risk of bleeding and transfusion (13). The decision regarding aspirin therapy is controversial. Neilipovitz et al. (14) modeled outcomes in infrainguinal vascular surgical patients using two strategies, one in which aspirin was continued and a second in which it was stopped 14 days before surgery. Continued aspirin use decreased perioperative mortality rates from 2.78% to 2.05% and increased life expectancy and quality-adjusted life expectancy by fractional amounts. However, aspirin also increased the number of hemorrhagic complications by 2.46%, primarily because of an increased incidence of non-life-threatening complications. Cephalosporin antibiotics that contain a methylthiotetrazole side-chain, such as cefamandole, cefotetan, moxolactam, and cefoperazone, have been associated with hypoprothrombinemia and bleeding and should used with caution for prophylaxis (15). Each surgeon must balance the risk of bleeding

against the potential benefit from continuing drugs that impair coagulation.

The surgeon's experience, the length of the operation, the patient's age, and preoperative hematocrit, the use of alternatives, such as autotransfusion, coagulation abnormalities, medications, and technical approaches all have an impact on bleeding in vascular surgery (16,17). Clinical and laboratory factors that play a role in the transfusion decision are discussed elsewhere in this text as are the major autologous blood strategies available to the vascular surgeon. Blood loss leading to transfusion is expected in specific groups of patients or types of procedures in vascular surgery. These include vascular trauma, (18–23) both ruptured and elective abdominal aortic aneurysm repair, (24–27) direct venous surgery, including thrombectomy and thrombolysis, (28–30) and thoracoabdominal aneurysm repair (31,32). Abdominal aortic aneurysm size has an impact on blood loss as well (Fig. 39.1). Reoperative procedures have a higher incidence of bleeding as well. Landry et al. (33) reported an estimated blood loss of 272.4+/−249.9 mL for redo lower extremity revascularizations compared to 174.8+/−140.8 mL ($P < .001$) for the original procedure. Injuries during orthopedic surgical procedures, (34) major-vessel resection in conjunction with urologic tumor resection, (35) and bleeding following cardiac catheterization and angioplasty (36) also carry a higher risk.

Although most individuals would associate trauma with blood loss and the need for blood replacement, the majority of trauma patients are managed without blood transfusion. A recent report of 5,645 patients treated in the year 2000 at the R. Adams Cowley Trauma Center in Baltimore, Maryland, reported that only 8% (479 in 5,645) of acute trauma patients received RBCs (37). Three percent received more than 10 units and accounted for 71% of all RBCs given.

Emergency, actively bleeding patients have a greater risk of complications and death than the elective patient. Mortality in the Maryland cohort was 39%. Of 64 patients treated by Jackson et al. (22) for abdominal vascular injuries, 23 (92%) died from hemorrhagic shock. Early action to control hemorrhage can have a significant impact on our ability to reduce allogeneic blood exposure in these patients and improve outcomes. Prompt diagnosis and timely surgical intervention directed at controlling hemorrhage are the mainstays of limiting allogeneic blood exposure in these situations. Early surgery for a leaking or ruptured abdominal aortic aneurysm can lead to a successful outcome in the majority of patients, while delaying leads to increased mortality (38,39).

Several reports of endovascular grafting (EVARs) in patients with ruptured or symptomatic abdominal aortic aneurysms validate that this approach leads to less blood loss and transfusion need (40–42). Van Sambeek et al. (43) reduced median blood loss from a mean of 3,400 mL for open repair versus 125 mL ($p = 0.010$) using the EVARs approach. Additional benefits of EVARs include shortened ICU and hospital length of stay and improved short and long-term survival. A prospective intent-to-treat protocol

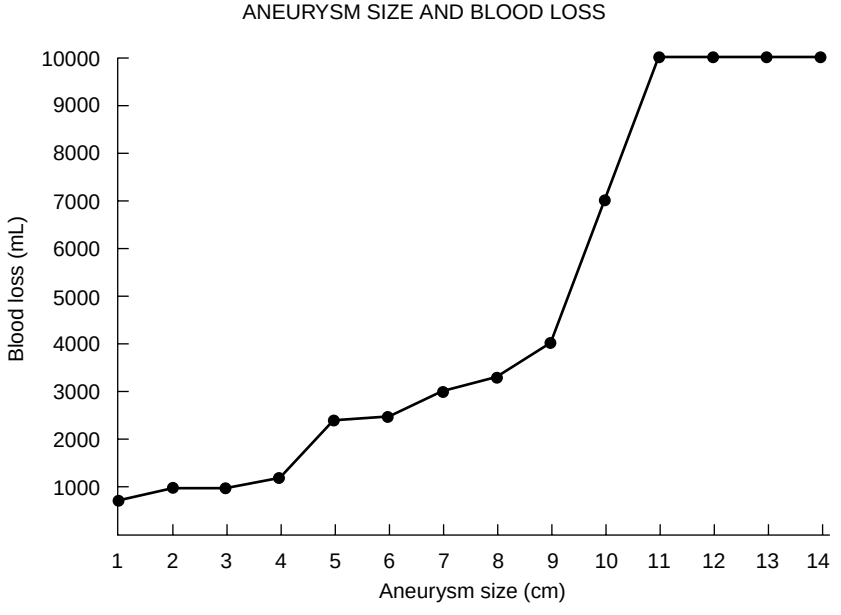

Figure 39.1 Influence of aneurysm size on blood loss. (Adapted with permission from Lord RSA, Hardman DTA, Margovsky A. Use of the cell saver in aortic aneurysm reconstruction. In: Tawes RL, ed. Autotransfusion: therapeutic principles and trends. Detroit, Mich: Gregory Appleton; 1997;151.)

for patients with ruptured or symptomatic abdominal aortic aneurysms showed that endovascular grafting was feasible in 32 of 40 (80%) patients. Volume of blood loss and transfusion need were significantly less compared to patients treated by conventional open surgical repair.

Transjugular intrahepatic portosystemic shunts (TIPS) have greatly reduced both initial bleeding from varices resistant to medical therapy as well as later rebleeding (44). Orloff et al. (45) has achieved 5-year, 10-year, and 15-year survival rates in 200 patients of 99%, 97%, and 95%, respectively by combining TIPS for variceal bleeding with careful, long-term follow-up.

Vascular injuries of the extremities are usually not exsanguinating unless left unattended. Ongoing bleeding can be controlled via direct compression and exploration to attain proximal control followed by either a direct repair or bypass (46). In some patients, peripheral vessel injury can be controlled with a stented graft (47). The use of a stent/graft combination to treat a traumatic femoral arteriovenous fistula has been described by Marin et al (48). Peripheral, aortopulmonary, and aortobronchial fistulae have been closed successfully with an endovascular approach, thereby controlling of hemorrhage and reducing transfusion need (49,50). Martinez et al. (51) used a saphenous vein covered graft to treat an expanding false aneurysm of the axillary artery.

Percutaneous puncture of the femoral artery using Seldinger technique has long been the standard approach to aortography and coronary angioplasty and has not been associated with major bleeding complications. However, larger diameter catheters and sheaths used in coronary angioplasty and stenting are associated with a higher rate of bleeding in the groin and into the retroperitoneum. Octagenarians who experience intraprocedural complications are at particularly high risk (52). The use of adjunctive glycoprotein IIb/IIIa receptor inhibitors has also increased the risk of bleeding (53). Fortunately, a variety of devices, ranging from sutures to plugs to sealants, are available to seal the femoral artery after puncture (54–60). Several comparative trials of these closure devices versus compression alone have proven their worth in reducing the incidence of hematoma, pseudoaneurysm, bleeding and the need for transfusion. They also permit earlier postprocedural ambulation (61,62).

The increased use of platelet inhibitors (see above) with coronary angioplasty has added a new group of patients at risk for bleeding and transfusion. Kinnaird et al. (52) identified 1,982 of 10,974 patients (18%) with bleeding complications after percutaneous coronary interventions (PCI). Five hundred eighty-eight patients (5.1%) had major bleeding and 1,394 (12.7%) had minor bleeding. Risk factors for major bleeding included the use of an intra-aortic balloon pump (odds ratio = 3.0, $p < 0.0001$), procedural hypotension (odds ratio = 2.9, $p < 0.001$), and age >80 years (odds ratio = 1.9 compared with age <50 years, $p = 0.001$). Bleeding was also an independent predictor of in-hospital death. Cote et al. (63) found an association between both major and minor bleeding in 2,559 consecutive patients who underwent percutaneous coronary intervention at Mayo Clinic, Rochester, Minnesota, between July 1, 1996, and April 30, 1998. Of those, 831 received abciximab and 1,728 did not. Major bleeding occurred in 18 patients (2.4%) who received abciximab and in 10 patients (0.6%) who did not receive abciximab ($P <.001$) (63).

Autotransfusion equipment should be ready for patients with acute bleeding so that as much shed blood as possible can be salvaged and returned. Even though the blood appears to have clotted, e.g., during repair of a ruptured AAA, such losses can be successfully salvaged, washed, and returned as red cells to the patient. An estimate of blood loss should be made early on so that appropriate replacements can be ordered from the blood bank. One should not be so foolish as to think that emergency vascular surgery can be done routinely without the use of allogeneic, or banked, blood.

The type of anesthesia and initial resuscitation fluid given to patients may have an impact on blood loss as well as outcome. Epidural anesthesia may result in less blood loss than general anesthesia (64). Waters et al. (65) noted an association between increased blood loss and the use of normal saline compared to Ringer's lactate in a double-blind study of 66 patients undergoing aortic reconstructive surgery. Patients treated with normal saline had more acidosis and blood product transfusion, but overall outcomes were the same for both groups.

Several studies have demonstrated that the adoption of transfusion guidelines, practice policies, and/or transfusion algorithms can bring some sense to transfusion practices while reducing the risk of exposure to allogeneic blood (66–71). The first step in this process is for the vascular surgeon to review his or her transfusion practices in order to get an understanding of which patients are transfused and how much blood is used (72). Blood losses should be calculated from retrospective personal data for patients having the same type of procedure, e.g., abdominal aortic aneurysm repair, to measure the range of the losses associated with the procedure. Table 39.1 shows an example of this calculation. With this information, the surgeon can establish a blood ordering schedule that will serve as a personal guideline for both allogeneic blood use and for instituting appropriate alternatives.

Unfortunately, transfusion practices in vascular surgery do not follow any clear standard. Surveys on blood product use in a variety of surgical procedures have consistently

TABLE 39.1
PERIOPERATIVE AND ALLOWABLE BLOOD LOSS

Step 1. Calculate perioperative blood loss

Perioperative blood loss equals the sum of transfused RBC volume (from all transfusions) and the blood loss from surgery to day 3 or 5 postsurgery.

RBC volume transfused + EBV × Hct Day − 1(before surgery) − EBV × Hct Day 3 or 5 (after surgery) = EBV (Hct D−1−Hct D+3) where the Estimated Blood Volume (EBV) is predicted from gender and body surface area.

EBV = Weight in kg × Average blood volume (ABV)

Age	Blood volume
Premature neonates	95 mL per kg
Full term neonates	85 mL per kg
Infants	80 mL per kg
Adult men	75 mL per kg
Adult women	65 mL per kg

Example: Perioperative blood loss

Your data for the last 10 female patients who underwent an open AAA repair show:

Average wt = 60 Kg
EBV = Wt × ABV = 60 × 65 = 3,900 mL

Average RBC volume transfused = 1,000 mL
Total allogeneic blood transfusion = 1,000 mL

Average Hct Day − 1 = 32%
Average Hct Day + 3 = 28%

Perioperative blood loss = RBC volume transfused + EBV × Hct Day −1 (before surgery) − EBV × Hct Day 3 or 5 (after surgery) = EBV (Hct D−1−Hct D + 3), or,

(1,000 + (3,900 × .32) = **2,248** − (3,900−(.32 − .28) = **156** = **2,092 mL**

Your average perioperative blood loss for an open AAA in a female patient is 2,092 mL (54% of EBV).

Step 2: Calculate allowable blood loss

$$\text{Allowable blood loss} = \frac{EBV \times (HCT_i - HCT_f)}{HCT_i}$$

Where Hct_i = Initial Hct and Hct_f = Final lowest acceptable hematocrit. Assume the final lowest acceptable hematocrit is 25%.

Example: Allowable blood loss

$$\text{Allowable blood loss} = \frac{3{,}900 \times (32 - 25)}{32} = 853\ ML$$

Step 3: Modification of practice to reduce allogeneic transfusion

Your current blood loss for this procedure in a patient with an initial Hct of 32% is 2,092 mL. If you accept a final hematocrit of 25%, you can safely lose 853 mL without the need for allogeneic transfusion. Your current losses minus acceptable losses equals 1,239 mL, the amount of blood you must account for to avoid transfusion.

Strategy 1: Raise preoperative Hct to 35% with iron and rHuEPO. Allowable blood loss becomes 3,900 × (35 − 25) / 35 = 1,115. Collect all shed blood using cell salvage and reinfusion to return 50% of losses = 1,046 mL. Your average blood loss of 2,092 is reduced by 1,046 mL, which equals 1,046 mL, which matches your limits of allowable blood loss.

shown extensive inter-hospital and surgeon-to-surgeon variability in both the types of patients transfused and the amount of blood given (73–76). Milne et al. (77) found that the majority of 31 vascular surgeons practicing in Scotland followed a blood ordering schedule for both elective and emergency surgery, typically using twice as much blood (eight units) for the latter type of case than for the former (77). Suenaga et al. (78) uses a transfusion index derived from an analysis of their experience in treating thoracic aortic aneurysm patients to estimate blood needs, but this type of practice is uncommon.

A report from the Mayo Clinic of transfusion practices in patients undergoing carotid endarterectomy exemplifies this approach and demonstrates its safety (79). One thousand one hundred fourteen patients who underwent carotid endarterectomy were stratified into 1 of 2 groups: (a) 1980 to 1985 (n = 552) and (b) 1990 to 1995. Perioperative transfusion rates decreased from 72.9% in 1980 to 1985 to 8.7% in 1990 to 1995 ($P < .001$). The number of units transfused to a patient also decreased from 1.10+/−1.30 U for Group 1 to 0.27+/−1.22 U for Group 2 ($P < .001$). Although patients were more anemic at discharge—hemoglobin = 13.7+/−1.4 g per dL in 1980 to 1985 to 11.8 +/− 1.5 g per dL—the incidence of stroke and perioperative cardiac events did not increase. The overall impact of such efforts awaits further randomized trials using appropriate outcome measures (80).

Intraoperative Aspects: Technique

The most common cause of intraoperative bleeding during vascular surgical procedures is probably surgical misadventure, such as inadvertent venous injury or the disruption of a friable, diseased vessel after clamp placement. This type of bleeding can be prevented only through careful surgical technique and experience. Dissection along anatomic avascular planes is essential and requires a thorough knowledge of anatomy. For example, dissection of the right common iliac artery should be done as close to its bifurcation into internal and external branches. Dissection at the iliac artery's take-off from the aorta increase the risk of injuring the underlying vena cava. All vascular structures should be clamped and tied before being cut. Any vessel inadvertently cut or any unexpected bleeding, no matter how minor, must be attended to or controlled. Attention to what may seem to be an insignificant detail at the time can lead to diminished blood loss. Blood loss from unattended small vessels during the course of an operation may build up gradually, especially in a hypertensive patient (81). A variety of cutting devices, including electrocautery, argon beam coagulators, ultrasonic dissectors, and lasers, can reduce blood loss in specific settings (82). In our experience, reduced blood loss is a function more of the surgeon's skill than of the device itself.

Modifying operative approaches may minimize blood loss in vascular surgery. Both the retroperitoneal approach to the abdominal aorta and the exclusion-bypass technique have been reported as superior to traditional surgical approaches and handling of the aorta in terms of blood loss, although some controversy exists. In their study of a standard transperitoneal approach, Leather et al. (83) estimated blood loss to be an average of 1,700 cc. By switching to a retroperitoneal approach and excluding the aneurysm, blood loss was decreased to 900 cc, a reduction of almost one half (83). Carrel et al. (84) observed a similar decrease, from 1,300 mL to 630 mL, in 42 retroperitoneal operations compared to 121 transperitoneal cases, as did Laohapensang (85) in 43 consecutive patients. In contrast, neither Cambria et al. (86) nor Sieunarine et al. (87) found a significant transfusion advantage to using one approach over the other in two series of 69 and 100 patients, respectively, randomized to either a retroperitoneal or transperitoneal operation. Lauder (88) proposed a midline laparotomy and right retroperitoneal dissection is an alternative exposure but this approach did not decrease blood loss.

Exclusion of the abdominal aortic aneurysmal sac prior to bypass has been used successfully by several groups of vascular surgeons to reduce intraoperative blood loss (89–91). In the author's experience, such an approach is useful for Jehovah's Witnesses. When coupled with a retroperitoneal incision, this procedure appears to result in less postoperative morbidity than a standard aneurysm repair. The value of a laparoscopic-assisted approach to abdominal aortic surgery in reducing blood loss is not yet known. Chen et al. (92) reported an average blood loss of one liter in 10 patients in whom he used this approach. In the lower extremities, Hans et al. (93) noted a greater blood loss with in situ femoropopliteal bypass versus using a reversed saphenous vein. They attributed this to an increased operative time and more release of blood when testing the vein.

Controversy exists over the benefit of using relatively impervious grafts to reduce blood loss. Woven Dacron grafts with minimal porosity, albumin-sealed and/or gelatin-sealed grafts essentially eliminate direct blood loss from extravasation during aortic bypass and replacement, but their effect on reducing transfusion need is questionable (94). Chakfe et al. (95) used albumin-impregnated polyester prosthetic grafts for abdominal aortic aneurysm repair in 218 cases (190 elective and 28 emergency) and in another 72 patients with occlusive disease of the aortic bifurcation. The overall incidence of transfusion was 40.4% and 42.6% in the two groups, with a mean of 1.4 units and one unit of red cells transfused, respectively. Barral et al. (96) obtained similar results in a randomized trial of high-density, knitted Dacron grafts versus identical grafts that were collagen-impregnated. Both authors concluded that impregnated

grafts did not significantly reduce perioperative blood loss or transfusion need. Reid and Pollock (97) reported that gelatin-sealed grafts had "no measurable blood loss at implantation". However, 47 patients still required transfusion for blood loss of greater than 750 mL or on clinical grounds. Fisher et al. (98) comparative analysis of double-velour, woven Dacron grafts compared to PTFE using sophisticated blood loss measurement techniques concluded that neither graft had an advantage over the other in decreasing blood loss or preventing transfusion. A significantly lower preoperative erythrocyte volume in the Dacron group may have accounted for increased transfusion need. It is difficult to determine the true benefit of impregnated grafts, since all of these studies suffered from lack of a consistent transfusion policy, which has an effect on overall transfusion rates. The amount of blood loss may depend as much on the surgeon as on the graft.

Endovascular grafting has gained a place in the treatment of abdominal aortic aneurysm. Multiple reports of endoluminal techniques document significant decreases in blood loss and/or transfusion need (Table 39.2) (99–104). Two reviews show the consistency over time of reduction of blood loss with endovascular grafting. Adriaensen et al. (102) reviewed nine studies that reported results of 1,318 procedures (687 endovascular repair and 631 open surgical repair). Mean blood loss was 456 mL for endovascular repair and 1,202 mL for open surgical repair ($P = .003$). Mahler et al. (105) later summarized 22 reports of open versus endovascular treatment of AAA, including some reported by Adriaensen, finding that blood loss was less, length of stay was shorter both overall and for the ICU and major complications were fewer. Figure 39.2 shows a mean reduction in blood loss of 466 mL reported for endovascular aortic aneurysm repair by 16 different groups. Comparative studies of open versus EVARs repair of abdominal aortic aneurysms demonstrated significant reductions in blood loss and transfusion need (99–104). All but one study showed reductions in blood loss from a median of 1,200 mL to 325 mLs. Chaikoff et al. (103) had similar losses of less than 500 mLs for both approaches. Three authors also report reductions in transfusion from 0% to 6% for EVARs versus 32% to 80% for open repair.

A trade-off with EVARs may be longer operating time, more local vascular or graft complications, and the need for more adjunctive procedures (105). The latter may increase blood loss as shown by Lee et al (106). Retroperitoneal procedures needed to treat small or aneuysmal iliac arteries increased blood loss up to two-and-a-half times in their patients (106). In inexperienced hands or with friable vessels, EVARs blood loss can reach levels of 2,500 mL—above that expected for a typical open aortic aneurysm repair. This reflects both the learning curve in this relatively new procedure and the fact that significant amounts of blood can be lost rapidly through a femoral artery insertion site. Endovascular grafting has also contributed to a reduction in blood loss in locations such as a retrohepatic inferior vena caval injury that are difficult to access (107).

Direct treatment of the aortic wall may facilitate surgical repair while reducing transfusion need. Chen et al. (92) have used direct application of a 25% glutaraldehyde solution to the aortic wall in five cases of aortic dissection 72. This approach strengthened the fragile aortic wall and helped prevent catastrophic bleeding caused by further perioperative aortic disruption.

Pharmacologic Agents Associated with Blood Loss

A variety of drugs that affect either blood loss or transfusion need are available to the vascular surgeon. These can be grouped by their intended action into broad categories of agents that limit blood loss, stimulate red blood cell regeneration, or serve as blood substitutes (Table 39.3). These are discussed in more detail elsewhere in the text.

TABLE 39.2
BLOOD LOSS AND TRANSFUSION NEED IN ENDOVASCULAR AORTIC SURGERY

Source	N Pts	Blood Loss Endo - mL	Blood Loss Open - mL	Trans Endo	Trans Open
Kibbe (99)	334	310 ± 19	1,590 +/− 124	6%	32%
Moor e(100)	573	400	800		
Gawenda (101)	31	300	1,000	0 mL	1000 mL
Adriaensen (102)	1318	456	1,202		
Chaikof (103)	236	457	432		
Patel (104)	51 age > 80 yrs.	225	2,100[a]	1 pt.	27 pts

[a]Significant to $p < .05$ or less.

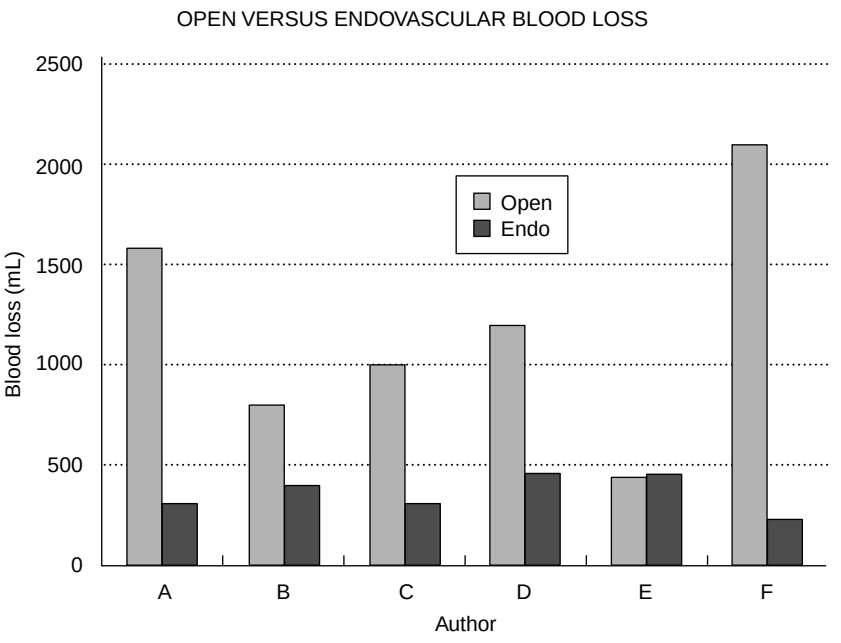

Figure 39.2 Mean blood loss with open versus endovascular AAA repair. A: (99); B: (100); C: (101); D: (102); E: (103); F: (104)

Vascular surgeons are familiar with the preoperative use of Vitamin K to correct a prolonged prothrombin time in a patient who has been taking warfarin. The drug, administered by intramuscular injection, restores normal clotting function within a few days by promoting the replacement of hepatic-derived clotting factors. Vasopressin can be used intraoperatively during portacaval shunting to reduce blood loss. An infusion of 0.4 units per min of vasopressin started prior to making the skin incision produces subcutaneous vasoconstriction and limits bleeding.

TABLE 39.3

PHARMACOLOGICAL AGENTS THAT AFFECT SURGICAL BLEEDING OR TRANSFUSION NEED

1. Limit blood loss
A. Vitamin K
B. Protamine
C. DDAVP
D. Tranexemic acid
E. EACA
F. Aprotinin
G. Factor VIII/IX
H. Recombinat factor VIIa
I. Vasopressin
J. Topical agents
K. Fibrin glue
L. Surgicel, Hemopad, etc.

2. Regenerate red blood cells
A. Oral fe
B. Intravenous fe
C. Erythropoietin
D. Steroids
E. Intravenous nutrition

3. Blood substitutes
A. Crystalloids
B. Colloids
C. Hemoglobin derivatives
D. Perfluorocarbons

Heparin is used in most vascular surgical procedures to prevent thrombotic complications. The dosage used may vary from one surgeon to another. Thompson and the Joint Vascular Research Group addressed concerns over the amount of blood loss and transfusion need associated with heparin use in a prospective multicenter study of 284 patients undergoing abdominal aortic aneurysm surgery (108). The patients were randomized to intravenous heparin or no heparin during surgery. Blood loss was similar for the two groups (median: 1,400 mL versus 1,500 mL of blood), as was the amount of blood transfused—4.0 units in both groups. The authors did observe a significantly higher incidence of fatal perioperative myocardial infarction in the non-heparinized group. One can conclude from this study that the risk of bleeding from heparinization is not great, but the risk of avoiding its use is. Ancrod may be useful in settings where heparin is risky. Cole et al. (109) demonstrated that the depletion of circulating fibrinogen with preoperative Ancrod was as successful as heparin in preventing graft complications and did not increase blood loss.

Many surgeons use protamine intraoperatively to reverse the effects of heparin during major cardiovascular surgery. The dose administered is calculated initially from the amount of heparin given and is titrated against clotting times. Jobes et al. (110) found that the titration and administration of protamine based on the specific

point-of-service measurement of coagulation factors resulted in less postoperative bleeding and decreased transfusion need (671 mL versus 1,298 mL), and fewer patients received transfusions (9/22 versus 18/24) with fewer donor exposures when compared to a conventional regimen. Despotis et al. (111) obtained similar results in 244 patients using an on-site, algorithm-driven monitoring system. Adding to the controversy is the report from Shore-Lesserson et al. (112) showing no differences in blood loss or transfusion requirements in 135 cardiac surgical patients.

Although protamine is given almost universally after procedures requiring cardiopulmonary bypass, there is no consistent pattern of use in aortic and peripheral vascular procedures when bypass is not employed (113). In these cases, heparin is usually given in smaller amounts based on body weight, and clotting times are rarely monitored. Some surgeons routinely use protamine after graft placement; others simply rely on heparin clearance to promote clotting. There is little information available on the role of protamine in preventing bleeding from heparin in vascular surgery. Dorman et al. (114) found that the use of protamine in a mix of aortic, infrainguinal, and carotid procedures did not reduce either blood loss or transfusion need. This group used systemic heparinization with 90 U per kg of body weight during surgery in 128 patients, randomizing them to reversal with either protamine or saline. No differences were found in either blood loss or transfusion requirements. Of interest is the finding that intraoperative bleeding following study drug administration was greater with protamine (318 + 33 ml versus 195 + 18 ml, $p < 0.05$).

A vasopressin analogue, desmopressin (1-desamino-8-D-arginine vasopressin, or DDAVP), has minimal vasopressor activity. Its potential usefulness during vascular surgery derives from its ability to elevate both factor VIII and factor VIII/von Willebrand Factor complex levels twofold to threefold over normal levels. DDAVP can add a significant advantage in the hemophiliac with a low factor VIII level (115). However, its role in surgical patients is controversial. Clagett (116) found no advantage in using desmopressin to reduce blood loss in his randomized study of patients undergoing aortic surgery. Lethagan et al. (117) reported a tendency toward a reduction in blood loss with the use of the drug in 50 patients undergoing surgery for aortoiliac occlusive disease, but the observed difference was not statistically significant when compared to the controls. The drug is not innocuous; it has a variety of side effects, which range from mild facial flushing and headache to tachycardia, hypertension and tachyphylaxis. Based on these studies and the extensive review and meta-analysis of the literature by Laupacis et al. (118), which concluded that desmopressin was of no benefit in reducing blood loss during cardiac surgery, the drug's role in vascular surgery is questionable. Desmopressin may have limited usefulness in correcting identifiable platelet defects, such as those caused by aspirin (119).

Aprotinin, or Trasylol, a serine protease inhibitor, has been used successfully to reduce blood loss during cardiovascular surgery in a number of clinical trials (120–122). The meta-analysis conducted by Laupacis et al. (118) concluded that aprotinin use resulted in decreased blood loss during cardiac surgery. Aprotinin is thought to work by inhibiting kallikrein and plasmin and/or by preserving platelet adhesion membrane receptors during cardiopulmonary bypass (123). Like desmopressin, aprotinin may play an important role in treating patients with aspirin-induced platelet abnormalities. Schonberger et al. (124) demonstrated significant reductions in both bleeding time and postoperative blood loss in aprotinin-treated patients who had received aspirin prior to coronary artery bypass. Experience using aprotinin in vascular surgical patients is limited but has shown similar results. From their study of aprotinin use in 136 aortic surgery patients, Ranaboldo et al. (125) were unable to conclude that there is any significant benefit in terms of reducing transfusion requirements, although they did observe reductions in both intraoperative and 24-hour postoperative blood loss. Lord et al. (126) have suggested that aprotinin may provide an additional benefit by minimizing neutrophil impairment following aortic procedures. Aprotinin must undergo further study to document both its safety and efficacy in vascular surgery before it is ready for general use.

Other pharmacologic agents may be helpful in reducing surgical blood loss. Epsilon-amino caproic acid (EACA) and tranexamic acid have been shown to be useful in reducing blood loss in cardiac surgery and liver transplantation (127–129). Bombesin, pentoxifylline, and prostacyclin are purported to act on the vascular system, bombesin by counteracting opioid-induced vasodilatation and pentoxifylline and prostacyclin by improving microcirculatory flow and tissue oxygen delivery (130). The clinical role of these drugs remains unproven, although the latter two may have some benefit in septic or critically ill patients who need to maximize peripheral oxygen consumption.

Recombinant human erythropoietin (rHuEPO) is not approved for use in patients with either cardiac or vascular disease because of concerns over potential drug-induced hypertension, cerebrovascular accidents and thrombotic complications. Most of this fear is based on early reports in renal dialysis patients (131,132). Some of these patients experienced shunt occlusion, probably from the effect of a rising hematocrit rather than from rHuEPO. Several large-scale studies of this drug in surgical patients have proven its value as an alternative to allogeneic transfusion (133,134).

There is little reported experience of the use of rHuEPO in vascular patients. The author has used rHuEPO successfully in a number of such patients who were Jehovah's Witnesses to restore red cell mass in both the preoperative and postoperative periods with none of the above adverse effects. It is important, when using erythropoietin, to make sure that the patient's iron stores are replenished, since existing iron is rapidly depleted. Iron dextran or polysaccharide infusions for replacing depleted iron stores can be used to treat acute critical surgical anemia (135). Iron dextran carries the risk of anaphylaxis and should be avoided whenever possible in favor of the safer polysaccharide products.

Fibrin glue is made by combining fibrinogen with bovine thrombin to produce fibrin (136,137). Generally, fibrin sealants are produced commercially from either processed human, animal, or synthetic sources but cryoprecipitate or platelet-rich plasma has been used. Fibrin glues adhere well to biological surfaces and have been shown to be effective in controlling bleeding in a variety of settings (138). Glimaker et al. (139) used fibrin glue to reinforce the sewn aortic stump in two patients who underwent removal of infected grafts. Others have used fibrin glue to repair myocardial lacerations and as part of septal defect repairs. Milne et al. (140) has found fibrin sealant to be an effective hemostatic agent when applied to suture lines and arteriotomies in a variety of vascular procedures. Several authors have reported successful sealing of iatrogenic arteriotomy sites with these products. Agus et al. (141) evaluated the usefulness of a ready-to-use hemostatic agent consisting of a collagen sheet coated on one side with human fibrinogen, bovine thrombin, and bovine aprotinin. Hemostatic control was considered good in 125 surgical operations, which included vascular, hepatic, and urological procedures. Fibrin sealant applied to the anastomotic site of PTFE Grafts to the femoral artery was compared to thrombin-soaked gelatin sponges in a single-blinded randomized prospective multicenter clinical trial of 201 patients. Time to hemostasis was shorter (median, 4.0 minutes; 95% confidence interval (CI), 3.8 to 4.18 minutes versus median, 5.6 minutes, 95% CI, 4.5 to 7.0; $P = .008$), and blood loss was less (mean, 4.0+/−29.7 g versus mean, 15.6+/−28.4 g; $P < .0001$) for the fibrin sealant treated patients (142). Unfortunately, fibrin glue derived from multiple allogeneic donors may be a source of disease transmission. Whenever possible, autologous plasma should be used rather than allogeneic plasma, if blood product exposure is to be avoided. Commercially produced virus-free sealants may solve this problem. Blood substitutes, whether perfluorocarbon-based or hemoglobin-derived, are currently undergoing clinical trials and are not available for general use. Initial reports of the utility of these agents as temporary oxygen carriers that provide a *bridge to transfusion* are encouraging (143,144). The determination of their usefulness in vascular surgery awaits further clinical trials.

ALTERNATIVES TO ALLOGENEIC BLOOD

Directed Donor Blood

Although patient preference is strong for the use of directed donor blood, its use does not reduce exposure to allogeneic transfusion, since this blood is allogeneic (145). Directed donor blood carries significant risks, including disease transmission and graft-versus-host disease (GVH). The use of directed donor blood may be an acceptable option in specific settings, such as neonatal or pediatric surgery, but for the most part, surgeons should discourage its use and instruct patients about its potential dangers.

Predonation of Autologous Blood

Autologous predonation is an alternative that can reduce dependence on allogeneic blood from 30% to 50% (146–148). Successful autologous predonation depends on (a) adequate time for donation; (b) a hemoglobin level greater than 11.0 g per dL; (c) the absence of significant patient disease, i.e., severe aortic stenosis or active angina; (d) the selection of appropriate patients based on anticipated blood loss and transfusion need; and (e) both patient and physician cooperation. The ideal patient for predonation is one who has an anticipated need for blood transfusion with a window of 2 or more weeks before surgery to donate, e.g., a patient scheduled for elective abdominal aortic aneurysm repair. Both Tedesco et al. (149) and Georgiev et al. (150) have used a combination of predonation and autotransfusion successfully in over 150 vascular patients to reduce allogeneic blood exposure. Baron et al. (151) combined predonation with the use of platelet-rich plasma to attain similar results.

The majority of patients can successfully complete a predonation program without incident. Relative contraindications to predonation include a history of congestive heart failure, valvular heart disease, recent myocardial infarction, angina, dysrhythmias, hypertension requiring multiple-drug therapy, seizures, or cerebrovascular disease. An increased incidence of reactions is associated with donor age under 17 years, weight over 110 lbs, female gender, and a history of previous reactions (152). Approximately 10% to 15% of patients are unable to reach the acceptable hemoglobin level of 11 g per dL for predonation. Treatment with recombinant human erythropoietin can facilitate predonation in mildly anemic patients scheduled for vascular surgery (153,154). Unfortunately,

predonation is rarely used in vascular surgical patients, although its ability to reduce allogeneic blood exposure has been clearly demonstrated. Only one of 31 surgeons in Milne and Murphy's survey used predonation (113). Similar results were found in Germany (155). Concerns over cost-effectiveness may limit its use, or vascular surgeons simply may not have considered predonation to be a safe alternative in their patients (156). The author prefers acute normovolemic hemodilution combined with cell salvage to predonation because the latter has the risks of transfusion error, is subject to storage defects and leads to an increased use of allogeneic blood.

Acute Normovolemic Hemodilution

There will be times when the surgeon will want to use autologous blood but will not have had sufficient time before surgery to schedule predonation. In such cases, autologous blood is still available in the form of acute normovolemic hemodilution if the patient is not anemic. The advantages of acute normovolemic hemodilution include an improvement in tissue perfusion secondary to decreased viscosity, and the loss of fewer red cells from bleeding. A decrease in viscosity produces an increase in cardiac output, primarily in response to an augmented venous return. Increases in cardiac output range from 25% to 35%, depending on the final hematocrit and the patient's tolerance for the procedure. Loss of blood with a hematocrit of 20% equates to less red cell mass depletion than loss of blood with a hematocrit of 30% or 40%.

Although hemodilution studies limited to vascular procedures are few in number, benefits have been shown both in terms of improved oxygenation and decreased reliance on banked blood (157–160). Parris et al. (161) reported an improvement in P50 in vascular patients intentionally hemodiluted with autologous blood when compared to those who received allogeneic blood. Hemodilution is most often used in combination with other techniques, such as autotransfusion (155). In his report of an extensive, 5-year experience in the treatment of abdominal aortic aneurysms using a combined approach of hemodilution, autotransfusion, and predonation, Hallett (162) suggests that hemoglobin levels of 8 g per dL and less are acceptable, providing that no symptoms or signs of myocardial ischemia appear and that the patient's hemodynamics remain stable. Others have reported similar successes using hemodilution as part of an overall approach to blood conservation that combines multiple techniques (163,164). The combination of preoperative use of erythropoietin to stimulate red cell production with hemodilution may help reduce the lead time and risk associated with autologous blood predonation (154). The addition of intraoperative cell salvage and return to these techniques provides a logical and readily accessible approach to blood conservation for the vascular surgeon.

Autotransfusion

Autotransfusion, or the collection and reinfusion of shed blood, is the most common form of autologous blood used in vascular surgery (165). This alternative has been demonstrated to reduce dependence on allogeneic blood by up to 75% of overall transfusion needs during vascular surgical procedures (166,167). Autotransfusion may be lifesaving in emergency vascular surgery when blood loss is high. Marty-Ane et al. (25) found that autotransfusion was the predominant intraoperative factor that correlated with decreased mortality in a series of 61 patients with ruptured abdominal aortic aneurysms. Shed blood can be collected postoperatively from thoracoabdominal aneurysm patients via mediastinal chest tubes. The ability of systems that wash shed blood to process small volumes (125 mL), together with their portability, make it possible to process small amounts of blood collected from wound drainage during the postoperative period in the ICU. It has been suggested by de Varennes et al., (168) based on a retrospective review of the charts of 338 patients, that the reinfusion of mediastinal shed blood following cardiac surgery limits the rate of postoperative reexploration for bleeding. Although this study suggests a role for postoperative autotransfusion beyond its impact on allogeneic blood use, this group's findings would need to be corroborated, especially since other surgeons have seen no impact on postoperative bleeding from autotransfusion (169).

However, cell salvage is not without controversy. Freischlag (170) has reviewed a number of reports of the value of cell salvage, finding that results are mixed in terms of both cost and avoidance of allogeneic blood transfusion. Cost has become an increasingly important issue in this age of managed care. Some surgeons have reduced their use of autotransfusion to save money (171). Others have found that a concerted effort to manage an overall blood-conservation program that includes autotransfusion leads to cost savings (172). Goodnough et al. (173) suggest that washing blood for autotransfusion becomes cost-effective only when blood losses of 1,000 mL or greater are encountered. Unfortunately, such blood loss can be predicted only in some cases, e.g., ruptured abdominal aortic aneurysms. As suggested earlier in this chapter, every vascular surgeon would benefit from a systematic review of his or her own blood loss for specific procedures to provide a basis for a rational cost-effective use of autotransfusion as well as other alternatives (174).

TABLE 39.4

A PLAN FOR TRANSFUSION ALTERNATIVES IN VASCULAR SURGERY

Step 1: Assess physician practice and hospital resources

Which procedures do you perform?
What is the blood loss for these procedures? For individual surgeons?
What alternatives are available, e.g., autotransfusion?
Devise strategy based on data analysis

Step 2: Initiate measures that cost little or nothing.

Good surgical principles
Modify transfusion trigger
Monitor and teach physicians
Hemodilution
Reduce phlebotomy

Step 3: Purchase, develop and utilize needed resources

Autotransfusion equipment
Aprotinin for selected cardiac cases
Set up rHuEPO program
Train physicians and staff

Step 4: Institute programs designed to reduce blood loss

Combined alternatives in CV surgery
Transfusion algorithms
Create bloodless medicine and surgery program

Step 5: Modify and fine-tune

Create database for real-time follow-up
Continue and fine-tune education
Listen, learn and contribute at national and international levels

SUMMARY

Successful transfusion strategies in vascular surgery are multifactorial and require an understanding of basic physiology, clinical patient characteristics, the impact of technique and medications on bleeding, and available transfusion alternatives. Table 39.4 provides a step-wise approach to planning for alternatives to allogeneic blood. Of primary importance is the vascular surgeon's individual attention to analyzing his or her transfusion practices. Coupling such data collection with appropriate knowledge can improve both transfusion practices and overall patient outcomes.

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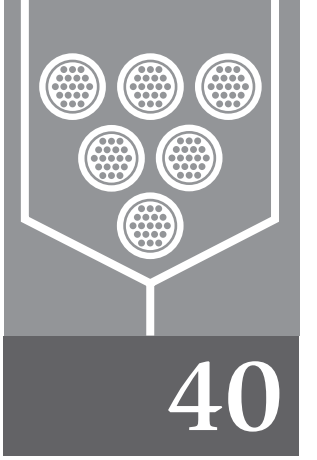

Solid Organ Transplantation

40

Nicolas Jabbour *S. Ram Kumar* *Singh Gagandeep*

The success of solid organ transplantation has permanently changed the outcome of patients with terminal organ failure. Significant advances in the technical approach to transplantation and immunosuppression have resulted in a steady rise in the number of organ recipients over the last few years. Transfusion therapy continues to be a critical feature of the support for solid organ recipients. An increased understanding of the immunologic issues surrounding organ transplants and the ability to manipulate the hematologic system of patients has resulted in other approaches to transfusion. This chapter will address the current status of transfusion therapy in solid organ transplantation and the risks and benefits of blood product use in these patients. Strategies currently in wide use at the authors' center for the realization of transfusion-free transplantation will also be discussed.

CURRENT STATUS OF PERIOPERATIVE TRANSFUSION DURING SOLID ORGAN TRANSPLANTATION

Blood product utilization during transplantation is routine and highly variable depending on the center and the organ transplanted (1). There is little published with regard to transfusion and blood product use during the entire perioperative period of solid organ transplantation.(2). According to UNOS data, in excess of 25,000 solid organ transplants were performed in 2003, and over 5,600 of these were liver transplants, associated with the highest routine blood use of any solid organ transplant. Consequently, transplantation places a huge demand on the blood product pool and conversely, transfusion therapy is a major issue in any transplantation program.

Several studies have tried to address factors that predict transfusion requirement during transplantation. Previous surgery has routinely been associated with greater technical difficulty and increased blood use in heart, lung, and liver transplants. During liver transplantation in particular, preoperative prothrombin time and degree of thrombocytopenia due to hypersplenism independently predict transfusion rates over four packed red cells (3). Intraoperative factors associated with increased blood product use include the duration of surgery, (3) specifically the duration of anhepatic phase, and the time to graft function (2). Although no one biochemical or patient-related factor can clearly predict transfusion needs in any organ transplant surgery, several studies have suggested that the perioperative team of physicians, i.e., surgeons and anesthesiologists, plays the single determining role in the utilization of blood products (3). That places the onus of a comprehensive understanding of the consequences of transfusion therapy and the means to favorably alter the outcome on physicians.

TRANSPLANT-RELATED TRANSFUSION—THE GOOD AND THE BAD

Benefits of Blood Transfusion in Transplantation

Transfusion of blood and blood products can be lifesaving in a variety of instances, particularly in high-risk patients debilitated by end-stage organ dysfunction undergoing major transplant surgery. Blood products are called in to use for improving hemoglobin levels and/or facilitating coagulation.

In addition, blood transfusion has a specific immune-modifying effect that has particular relevance in the transplant recipient. In their seminal paper, Opelz et al. (4) showed that blood transfusion increased renal graft survival and demonstrated subsequently that this response was transfusion dose-dependent, (5) while white cell-depleted red cells were not as effective in promoting graft survival. The exact cause of this favorable effect remains unknown. Transfusion-associated immunosuppression has been well documented and favorably utilized in other conditions, such as in women with recurrent abortions who shared a HLA type with their husbands (6). Similar suppression of cytotoxic T-lymphocytes may play a role in graft survival (7). Other suggested mechanisms include the development of anti-idiotype antibodies, (8) or pretransplant selection, in that transfusion protocols eliminate from the transplant pool sensitized patients who are more likely to have graft failures (2). These results led to the consideration of blood transfusion as a strategy to improve graft survival in transplant recipients.

With the rapid improvement in immunosuppression therapy, the additional effect of transfusion became marginal and more recent experience suggests no difference in graft survival between transfused and nontransfused organ recipients (9). Subsequently, more specialized protocols, such as donor-specific peri-transplant transfusion and transfusion combined with immunosuppression were utilized in one haplotype misidentity transplants to improve graft survival (10,11). However, the continuing improvement in HLA technology and remarkable advances in targeted and safe immunosuppression have further diminished the relevance of such protocols in clinical practice. The increased understanding of the adverse effects associated with transfusion has now tilted the balance against the small and purported benefit seen with their use in solid organ recipients.

Adverse Effects of Blood Transfusion

Immunohematologic Complications

Hemolytic transfusions are reported in approximately 1 in 6,000 units transfused and fatalities associated with approximately 1 in 100,000 units (12). ABO incompatibility occurs at a rate of 1 in 33,000 and acute anaphylaxis at 1 in 20,000 to 50,000 (14). Transfusion-related acute lung injury (TRALI) occurs in 1:2000 transfusions. This is a multifactorial immune-mediated complication of blood transfusion that is associated with all blood components. Of particular relevance in the immunocompromised transplant recipient is the even less frequent graft-versus-host-disease (GVHD) that can result from blood transfusion (15). Transfusion of blood products that contain immunocompetent T lymphocytes, especially from partially HLA-matched donors such as first-degree relatives, leads to a systemic immunologic reaction characterized by fever, diarrhea, skin rash, leucopenia, and thrombocytopenia, and is invariably fatal. Although gamma irradiation of cellular blood components may reduce the incidence of GVHD, the logistics are daunting in transplant recipients who could require large volumes of blood products in short durations of time (2).

Immunomodulatory Effects and Its Consequences:

Multiple studies in vitro have documented that transfusion results in a modification of recipient blood components, which can suppress host immunity. Transfusion decreases the number of CD4 lymphocytes, natural killer cells, and antigen-presenting cells, and may also suppress monocyte function and the trafficking of granulocytes to sites of infection (13). Following transfusion of at least two units of allogenic blood, the serum of patients begins to show a significant increase in vascular endothelial growth factor and a concomitant drop in endostatin, thereby rendering it favorable for angiogenesis, as noted by a significant increase in vitro in endothelial cell proliferation and whole assay angiogenesis (19).

Several studies have observed adverse clinical consequences, presumably related to this immunomodulatory effect of blood product transfusion. Homologous blood transfusions are associated with a significantly increased incidence of acute respiratory distress syndrome, (20) postoperative bacterial infection, (21,22) and ventilator-associated pneumonia (23). After correcting for baseline hemoglobin levels and severity of illness, blood transfusion has a strong correlation with prolonged hospitalization and increased mortality (20). In particular, the subgroup of liver transplant recipients that require transfusion of more than four units of packed cells have significantly reduced one-year survival (24). When transplantation is undertaken in patients with early malignancy, there is at least a theoretical, albeit controversial, concern that perioperative blood transfusion correlates with cancer recurrence (25).

As discussed in greater detail elsewhere in this book, blood is a precious fast-depleting commodity that is associated with a sizeable price tag. Given the large volumes of blood products involved in solid organ transplantation, the financial burden from the direct and indirect costs associated with transfusion and the social burden due to the imbalance in demand and supply are significant. Further, the risk of pathogen transmission with blood transfusion is a particular concern in transplant recipients who are on high dose immunosuppression therapy.

TRANSFUSION-FREE TRANSPLANTATION

Kidney and pancreas transplantation are routinely performed without the utilization of blood products. With improvement in techniques and refinement in approaches during cardiopulmonary bypass, several lung and heart transplants have also been completed without blood products (2). The technical challenges associated with liver transplantation and the hematologic and coagulopathic effects of liver failure make transfusion-free liver transplantation a major challenge. The need to perform high-risk surgical procedures, traditionally associated with major blood losses in Jehovah's Witness patients, who refuse blood products on religious grounds, stimulated an intense evaluation of alterative approaches to transfusion. At the author's institution, the extrapolation of well established principles from major surgeries in Jehovah's Witness patients to liver transplantation, has significantly limited, and even eliminated in some instances, the need for blood product utilization (26). For the realization of transfusion-free transplantation, patient optimization begins even as they wait for organs.

Preoperative Optimization

Hematologic Parameters

It is imperative that the integrity of the hematologic system be extensively evaluated prior to surgery just as the cardiovascular or respiratory systems. Multivariate analyses in various studies have shown that preoperative hemoglobin levels (27) and prothrombin time–international normalized ratios (PT/INR) (3) independently predict the need for blood product utilization.

Anemia, with a wide array of causative factors like chronic disease, malnutrition, iron deficiency, hemolysis etc., can be a particular challenge to manage. One of the preferred approaches to managing preoperative anemia is directly enhancing the patient's red cell mass, which, in many ways, can be considered equivalent to autologous donation without the use of blood banking. By carefully and adequately stimulating the erythropoietic machinery, patients can produce in excess of one gram of hemoglobin (equivalent to one unit of red cells) per week (28). In order to achieve bone marrow stimulation, it is important to provide the marrow with the necessary elements for synthesis. Recombinant human erythropoietin (rHuEPO) has now gained widespread use in order to enhance red cell production, especially before undertaking major operative procedures in Jehovah's Witnesses patients (29,30). Subcutaneous rHuEPO given every 72 hours is a convenient and cost-effective way to maintain effective stimulatory levels in blood and enhance reticulocyte responses, (31) even in the presence of malnutrition, liver disease, or portal hypertension. In our own experience with three Jehovah's Witness patients with end-stage liver disease and major upper gastrointestinal variceal bleeding, hematocrit levels have been elevated from a low of 16% to 48% within 3 months prior to surgery. During enhanced rHuEPO-driven erythropoiesis, physiologically normal amounts of mobilizable iron are frequently insufficient to meet the needs of the expanded pool of transferrin receptors on red cell precursors, resulting in functional iron deficiency (32). Iron requirements (in milligrams) can be estimated by multiplying the factor of 150 by the amount of desired elevation in hemoglobin (in g per dl). Pretreatment iron stores can be evaluated by measuring serum iron, total iron binding capacity, transferrin saturation, and ferritin levels. A functional iron deficiency occurs when transferrin saturation falls below 20%, the serum ferritin declines to less than 100 µg per L, or the proportion of hypochromic RBCs rises above 10%. Both enteral (200 mg doses of oral elemental iron, or 900 mg of iron sulfate) and parenteral routes (200 mg per week of intravenous iron dextran or saccharate) of supplementation can be used, the latter being reserved for patients in whom the enteral route does not meet the requirements or is poorly tolerated (33). Furthermore, vitamin B12 and folate levels must also be monitored and supplemented as necessary during rHuEPO therapy.

Similarly, coagulation abnormalities need to be effectively addressed preoperatively, which will also help limit preoperative blood losses. Clotting disorders as a result of vitamin K deficiency secondary to biliary obstruction or long-term parenteral nutrition, for example, should be alleviated via supplementation. When coagulopathy due to liver disease prevents response to this intervention, components of the clotting pathway may need to be directly replenished. Recombinant activated human factor VII (see below), which is approved for use in hemophiliacs with inhibitors to factor VIII, may need to be used off label in the occasional preoperative patient with persistent and significant hemorrhage, for example, a coagulopathic Jehovah's Witness patient with a major gastrointestinal bleeding episode, (34) or following interventions such as biopsy etc. (35).

Nutrition

Stephenson et al. (27) categorized 99 patients with end-stage liver disease requiring liver transplantation into mild, moderate, and severe malnutrition based on subjective global assessment of nutritional status. After correcting for several patient variables such as age, sex, platelet count, serum creatinine, and hemoglobin levels, those with severe malnutrition were found to require significantly more packed red cell transfusion than those in the mild and moderate categories. Therefore, nutritional support, which can be achieved with

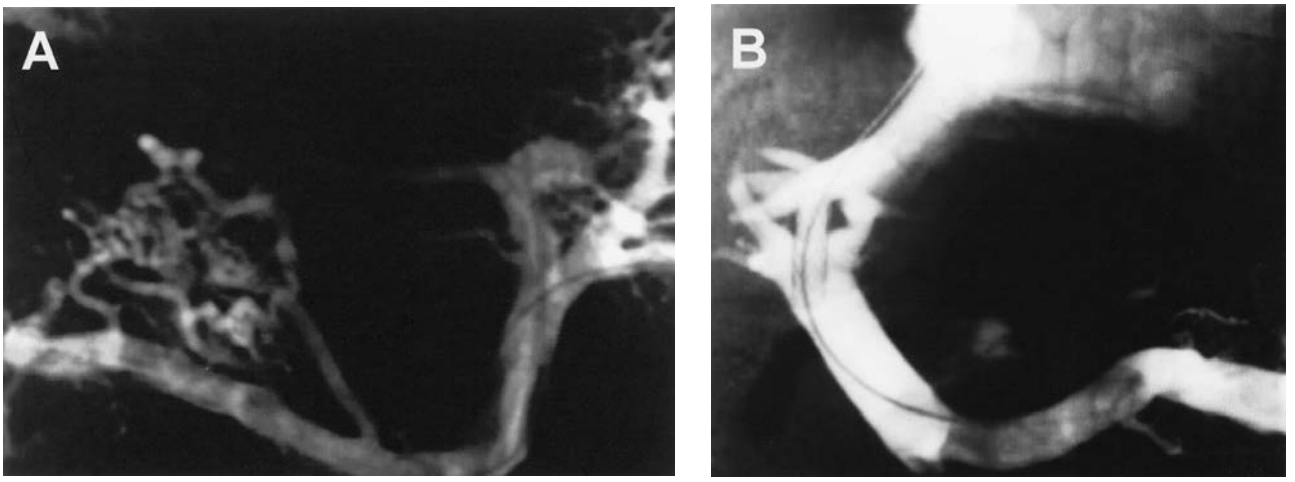

Figure 40.1 A pretransplant Jehovah's Witness male with end-stage liver failure had recurrent upper gastrointestinal bleeding from significant portal collaterals (A). Following TIPS, there is a dramatic reduction in collateral flow (B).

relative ease in a majority of ambulatory pretransplant patients, is bound to have a significant impact on their transfusion requirements during transplantation. Not infrequently, extensive attempts using both the enteral and parenteral routes may not help the nutritional status in patients whose liver is deteriorated to the point of being unable to assimilate the energy supplementation.

Preoperative Blood Losses

Minimizing preoperative blood loss may be just as important as the correction of anemia. This would imply an aggressive and definitive therapeutic approach to esophageal variceal bleeding. A discriminatory use of Transjugular Intrahepatic Portosystemic Shunt (TIPS) may also be indicated in select cases of severe portal hypertension. TIPS have been occasionally used prophylactically in Jehovah's Witness patients with extensive varices (Fig. 40.1). Such an approach needs to be weighed against the less frequent but major complications, such as bleeding, hepatic encephalopathy, etc., (36) with the realization that TIPS may not have a significant effect on thrombocytopenia from hypersplenism (37).

Intraoperative Approach

Following is a discussion of some of the cardinal principles and technological advances that when utilized intraoperatively minimize blood loss and preclude the need for transfusion.

Acute Normovolemic Hemodilution (ANH)

ANH involves the collection of blood and its replacement with a colloid and/or crystalloid infusion followed by reinfusion of the collected blood at the conclusion of the surgery. By inducing a moderate isovolemic (38) anemia during surgery (Fig. 40.2), the blood lost is diluted and by withdrawing and later reinfusing whole blood, ANH

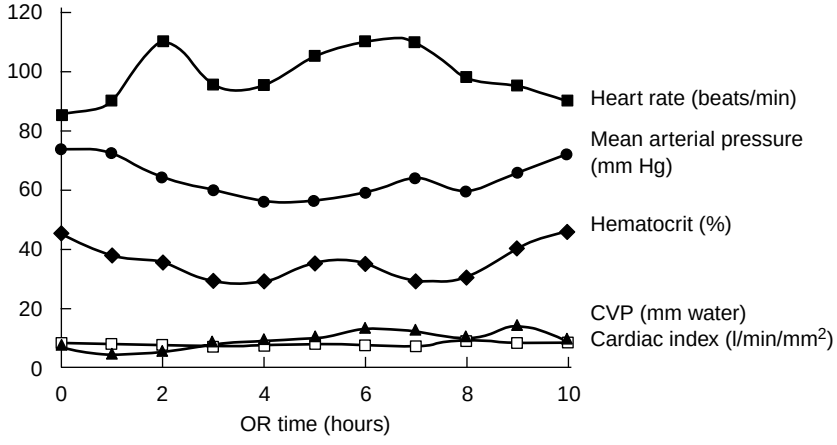

Figure 40.2 Relatively preserved physiologic parameters during acute normovolemic hemodilution in a patient undergoing live-donor liver transplantation. CVP, central venous pressure.

spares not only the red cell mass but platelets and clotting factors as well. ANH offers a few advantages over preoperative autologous donation (PAD). To begin with are the added benefits of greater convenience and reduced expense. Blood collection as part of ANH is performed only once, on the day of surgery, whereas PAD can involve multiple clinic visits depending on the quantity of blood desired. This additional administrative cost when coupled with the extra expenditure associated with discarded or unused blood units (39) diminishes the appeal of PAD. PAD does not guarantee against clerical errors or mishandling leading to a host of other complications. Furthermore, the quality of blood used in PAD can often be compromised in manners that are unlikely to occur within ANH. For example, stored blood has reduced 2, 3 diphosphoglycerate levels and other biochemical alterations which can reduce the ability of oxygen unloading. Finally, ANH has the potential of gaining acceptance among Jehovah's Witnesses because collected blood can be kept within an extracorporeal circuit that is in continuity with the patient. The authors currently use ANH routinely not only in Jehovah's Witness patients, but in most adults who do not have coexisting cardiovascular disorders during major hepatobiliary and pancreatic resections as well. A recent internal data review (unpublished personal observations) revealed a significant reduction in the use of blood products at our institution following the widespread utilization of ANH.

Intraoperative Cell Salvage (ICS)

ICS serves as an effective tool in blood conservation by allowing the retrieval and reuse of blood lost in the operative field. Electron microscopy reveals only minor alterations in red cell morphology with ICS, (40) and red cells maintain near normal survival (41) and 2,3 diphosphoglycerate concentrations (42). ICS is regarded as a reliable method of autotransfusion and is embraced even by Jehovah's Witness patients if administered via a contained system continuous with the patient at all times. Studies have documented successful application of the principles of ICS to liver transplantation with reduction in the need for allogeneic blood (43).

The use of ICS, however, brings with it a fresh set of considerations prior to its integration into any program. Significant controversy surrounds the relative benefits of the use of ICS when weighed against the cost associated with the cell-saver device, associated components and disposables, and the services of a perfusionist (44,45). In a study of orthotopic liver transplants, Kemper et al. (46) compared the cost of intraoperative blood salvage based on the duration of the surgery with the absolute cost of transfusing equivalent amounts of allogeneic packed red cells. On an average, autologous ICS cost $1048 per patient, while an equivalent amount of allogeneic blood was calculated at $429 per patient. Their case-by-case analysis revealed that in only three patients (4.8%) who received between 16.4 and 46.6 units of recycled cells did the use of ICS result in cost savings. Several studies have looked at restricting ICS to specific high blood loss surgery (47) versus setting up economic models wherein the services of the equipment and perfusionist are variably outsourced (48) to offset the financial burden. In reality, the cost analysis of ICS is complex and depends on a variety of factors including the type of cell salvage device, the nature of surgical procedures, amount of blood loss, annual caseload, etc. More importantly, studies of cost are an index of the direct financial burden. What cannot be included in these analyses is the overall price of allogeneic blood transfusion, far more important than the mere cost of it. It is universally accepted that ICS can ease the burden on the need for blood products and in this regard, the authors submit that it may even lead to an eventual financial benefit.

Another important consideration with the use of ICS is that only red blood cells are salvaged. The blood that is recycled is depleted of clotting factors and platelets. Large volume ICS may, therefore, lead to a coagulopathy if clotting factors are not appropriately replenished. If heparin is used in the ICS circuit to prevent clotting, the returned blood cells must be washed carefully of any residual heparin. Some of the other complications associated with the use of ICS include air embolism, infection, and DIC. In order to minimize these risks, ICS is contraindicated when concomitant intra-abdominal infection is suspected and in transplant cases with potential for contamination with gastrointestinal fluid. Certain local clotting agents, such as gelatin sponges, powders, or collagen hemostatic material should also be avoided in conjunction with ICS.

Lastly, there is some concern, at least from animal studies, (44) that ICS may result in systemic dissemination of malignant cells. Human studies have failed to corroborate these findings, (50) and there are suggestions that the application of specific techniques such as irradiating salvaged blood (51) or the use of leukocyte depletion filters (52) may further limit the spread of malignant cells. Caution is still recommended with the use of ICS in patients undergoing transplantation for early malignancies, and balancing the risk of malignant dissemination against that of severe life-threatening anemia in a Jehovah's Witness patient, for example.

Coagulation Management

Transplantation of the heart, heart and lungs, and liver, in particular, place a significant burden on the patient's coagulation system. While cardiopulmonary bypass for heart

transplant requires systemic anticoagulation and results in bypass-related platelet and coagulation dysfunction, the anhepatic phase in liver recipients results in fibrinolysis, further taxing an already suboptimal coagulation system. Immediately after the implanted liver is perfused, a more severe coagulopathy is frequently seen probably related to ongoing fibrinolysis, or the release of donor heparin, or heparinlike substances from the liver itself (2). Hence, an understanding and optimization of the coagulation system during transplantation are essential to minimize blood loss. This approach must go beyond the standard coagulation tests, such as PT, PTT, and platelet count, which reflect the quantity of clotting factors but convey little in regards to the quality of clot formation. For example, the diagnosis of fibrinolysis, a major cause of persistent coagulopathy unresponsive to conventional treatment in liver transplant patients, cannot be made by the usual coagulation tests, mandating the need for a thromboelastogram.

Until recently, the correction of coagulopathy implied the infusion of blood products such as FFP, cryoprecipitate, and platelets. Recently, significant inroads have been made into the understanding of and ability to manipulate several other factors that play a major role in enhancing coagulation. The use of epsilon aminocaproic acid may serve to control ongoing bleeding in liver recipients due to reticent fibrinolysis. Similarly, the effectiveness of aprotinin has been evaluated in orthotopic liver transplantation in a multicenter randomized study (53). Porte el al. (53) divided 137 patients with similar clinical characteristics, preoperative laboratory parameters, and surgical variables into three groups based on preoperative administration of high dose aprotinin, regular dose aprotinin, or placebo. Both high dose aprotinin, which served to inhibit kallekrein, and regular dose aprotinin, at a plasmin inhibiting level, were administered at a loading dose of $2 - 10^6$ kallekrein inhibiting units (KIU) followed by an infusion of 1×10^6 KIU per hr and 0.5×10^6 KIU per hr, respectively, until 2 hours after graft reperfusion. Aprotinin administration resulted in significant reduction in blood loss by 60% in the high dose group and 44% in the regular dose group ($p = 0.03$), with a concomitant fall in the need for homologous and autologous blood ($p = 0.02$) and blood products ($p = 0.01$).

The majority of clotting factors is synthesized by the liver, and factor VII (FVII), with the shortest half-life, is depleted most rapidly in liver failure. Hence, intuitively, replenishing FVII should favor coagulation. Recombinant activated factor VII (rFVIIa), extracted from transfected hamster kidney cells, is characterized by an amino acid sequence and biological activity that is identical to activated human FVII. rFVIIa binds to exposed tissue factor at sites of injury only, thereby promoting the formation of a localized clot, without increasing the risk of systemic thrombosis. In an open-label, pilot study on six patients undergoing liver transplantation, the use of a single 80 μg per kg dose of rFVIIa significantly reduced blood loss and the requirement of both packed red cells and fresh frozen plasma (54). Our own experience with the successful use of rFVIIa in 10 Jehovah's Witness patients (unpublished personal observations) with decompensated cirrhosis undergoing liver transplantation corroborates the published findings. Although a theoretical concern exists of developing a prothrombotic state with the use of such potent clotting factors in the setting of fresh vascular anastomoses in transplant patients, evidence seems to suggest that, in reality, such a situation is at the least infrequent.

Physician-Related Factors

The surgeon's and anesthesiologist's experiences and attitudes are some of the most significant predictors of transfusion requirements during transplantation (3). As long as a patient's hemoglobin is sufficient to provide tissues with adequate oxygen, the only indication for blood transfusion is to replace operative blood loss and is not a therapeutic goal in itself. Of all the indications for intraoperative blood product utilization, the majority is related directly to the amount of blood lost. In the authors' opinion, surgeons are the only health care providers that can effectively decrease the usage of blood products. Perioperative decision making and judgment, apart from the surgical technique itself, are therefore crucial to successful outcomes.

Sound decision making involves flexibility and the acknowledgment that operative procedures need not proceed under unfavorable circumstances. Under conditions of foreseeable uncontrolled hemorrhage, for example, other methods and approaches must be pursued. The authors have published their unusual experience in a 35-year-old Jehovah's Witness male with end-stage liver disease (55) secondary to primary sclerosing cholangitis (Fig. 40.3). Prior gastrointestinal bleeding from esophageal and gastric varices had reduced the patient's hematocrit to 16%. TIPS, rHuEPO, folic acid, and iron supplementation raised the hematocrit to 49% and the coagulation parameters were corrected prior to a scheduled live-donor liver transplant. Intraoperatively, an unusually large left lateral segment of liver adherent to the spleen was encountered. Attempts to ligate the upper polar branch of the splenic artery led to significant hemorrhage from peri-splenic collaterals. Consequently, the authors decided to approach the procedure in stages. At this stage, a partial hepatectomy was performed and the donor lobe was successfully implanted. Despite the blood loss, the patient's hematocrit at the end of surgery was 45%, due to the judicious intraoperative use of ANH and cell-saver techniques. With recovery of the implanted liver, the patient's coagulopathy spontaneously

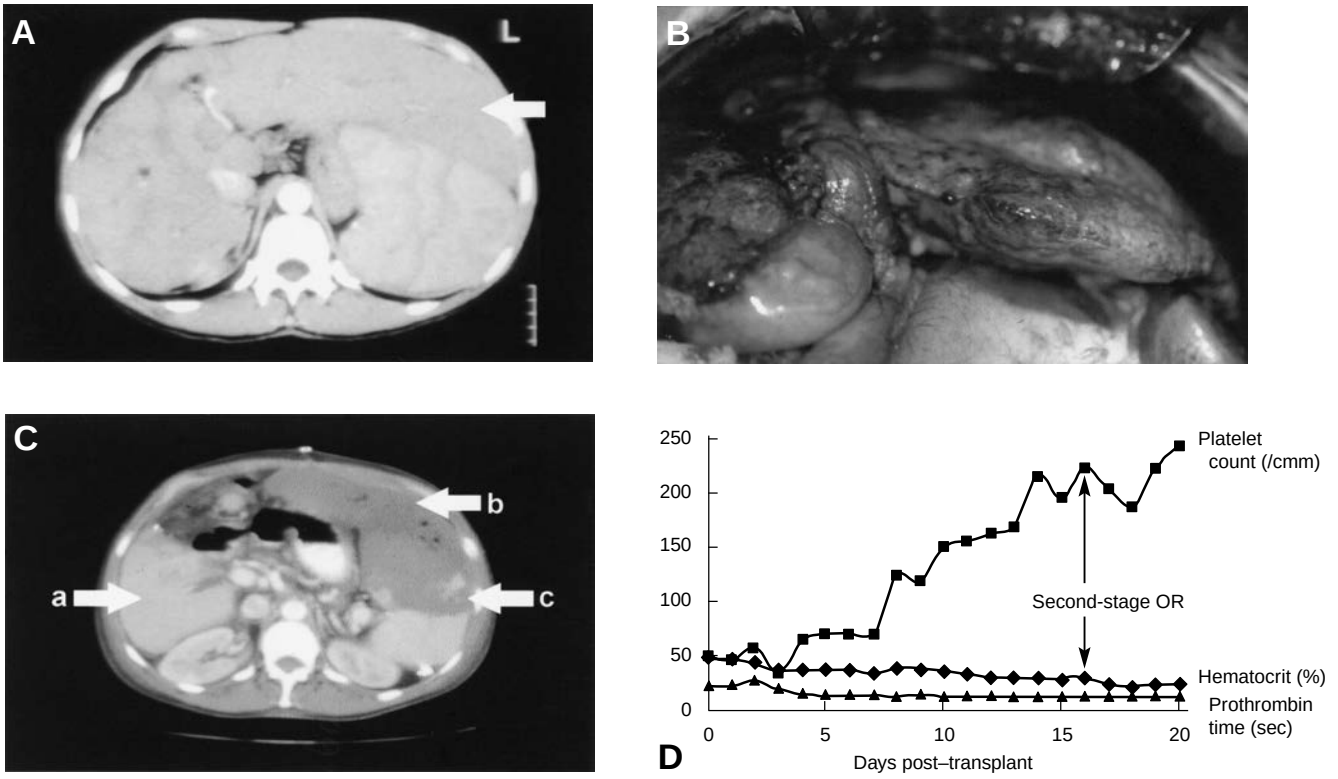

Figure 40.3 Staging hepatectomy during live-donor liver transplant in a Jehovah's Witness recipient. This 35-year-old male was in end-stage liver failure due to primary sclerosing cholangitis. A preoperative CT scan (A) demonstrates a large left lateral segment of the liver (arrow), which was confirmed at surgery (B). Due to severe hemorrhage from splenic collaterals during hepatectomy, the procedure was staged. A partial hepatectomy was performed. Postoperative CT scan on day 15 (C) showing the transplanted right lobe of the liver (a), the devascularized left lateral segment of the cirrhotic liver (b) and the ischemic upper pole of the spleen (c). Following recovery of the implanted liver and improvement in the hematologic and coagulation parameters (D), the patient was taken back to the operating room for completion hepatectomy and partial splenectomy. The patient had an uncomplicated recovery. (Modified with permission from Jabbour N, Gagandeep S, Mateo R, et al. Live donor liver transplantation: staging hepatectomy in a Jehovah's Witness recipient. *J Hepatobiliary Pancreat Surg*. 2004;11:211–214.

corrected and platelet count recovered. In 2 weeks, the patient was taken back for completion hepatectomy and partial splenectomy. Notwithstanding a complicated course and a major surgical undertaking, the patient was discharged in 3 weeks with completely normal liver function, without the administration of any blood products.

In order to provide a safe transfusion-free transplantation, the surgical technique should be driven by a zero tolerance for blood loss of any kind. Precise technique and meticulous hemostasis must be the cornerstones of the surgical procedure. The patient's coagulation system should not be relied upon, and simple physical packing, even of minor bleeding, should not be considered sufficient. Resorting to more dependable measures such as argon beam electrocautery, suture ligation, and so on is recommended.

Also vital to the management and maintenance of a patient's hematologic system is clear communication with the anesthesiologist. The role of the anesthesiologist in blood management is critical, especially given their involvement in ICS and ANH. The explicit goals of anesthesia during transfusion-free transplantation should include the maintenance of normovolemic status and the potential need for hyperoxic ventilation and controlled hypotensive anesthesia. For example, a low CVP can markedly reduce blood loss during parenchymal transection of the liver. Avoidance of hypothermia can help prevent temperature-related coagulopathy.

Postoperative Care

Appropriate postoperative management of the hematologic system begins with prevention and early recognition of blood loss. Any sudden drop in hematocrit or ongoing blood loss from drains should warrant consideration of

active bleeding and be dealt with promptly. Needless workup, including laboratory testing, should not delay institution of appropriate interventions. Phlebotomy represents a major and under-appreciated source of blood loss, especially in the intensive care setting. Restricting investigations to the absolutely essential, avoidance of blood draw from large bore or high-flow lines and minimizing the quantity of blood drawn (56) by using pediatric collection tubes, for example, can significantly limit iatrogenic postoperative anemia. There is an increasing body of evidence that moderate degrees of anemia are well tolerated by a majority of postoperative patients in the absence of cardiovascular impairment. Following established guidelines for transfusion based on physiologic endpoints and overall clinical status rather than arbitrary single-point hemoglobin values has been shown to improve patient outcome. rHuEPO may also be used postoperatively to improve red cell mass (57).

Additional goals that complement reducing blood loss and improving hemoglobin levels in the postoperative period include augmenting oxygen delivery and reducing oxygen consumption. Oxygen delivery can be improved by increasing the fractional inspired oxygen concentration (via supplemental oxygen, mechanical ventilation, or hyperbaric oxygen), maintaining adequate intravascular volume and optimizing cardiac performance. Appropriate cardiac and respiratory support, control of fevers and shivering, and bed rest with sedation, or complete paralysis in selected instances, can help minimize oxygen consumption. Anecdotal experience with a 65-year-old Jehovah's Witness male admitted to our center for a cadaveric liver transplant reaffirms this concept. Preoperatively, the patient was markedly coagulopathic and anemic due to severe liver disease and hepatorenal renal syndrome, for which the patient underwent intraoperative dialysis. Postoperatively, the hematocrit fell to 13% and remained refractory to rHuEPO, iron, and folic acid supplementation. The patient had repeated episodes of life-threatening arrhythmias refractory to medications. Consequently, a tracheostomy was performed with continuous ventilatory support, followed by hematocrit rising to 20% within 2 weeks and arrhythmias were fully controlled without medication. The patient was discharged 3 months after the transplant with normal liver and kidney function. This case illustrates the need for careful balance between oxygen delivery and consumption. Once delivery is limited, attention should be diverted to curtailing consumption.

Application of the aforementioned principles to liver transplantation as part of the Transfusion-Free program at the University of Southern California has met with considerable success. The authors recently reviewed 38 live-donor liver transplants performed at their institution between 1998 and 2001, (26) including eight transfusion-free (TF group) and 30 transfusion-eligible (TE group) patients. All donor hepatectomies were completed without any intraoperative complications or the use of blood products. While 80% of TE patients received a median of 4.5 ± 3.5 units of packed red cells, blood products were completely avoided in patients in the TF group by utilizing the transfusion-free principles reviewed here. Patients in the TE group had a significantly higher hematocrit preoperatively following careful stimulation of their bone marrow. All other variables like preoperative liver disease severity, hospital course, including operative times and hospital stay, and survival were comparable between the two groups. The advent of live-donor liver transplantation has further expanded the possibilities of performing transplants prior to the onset of end-stage liver disease and therefore, increased the feasibility of achieving favorable outcomes. These principles have also successfully been applied to liver-donor pediatric liver transplantation (58). Two Jehovah's Witness children, 6 months and 3 years of age had end-stage liver disease secondary to biliary atresia. The first patient had undergone a Kasai procedure followed by rapidly deteriorating liver failure and gastrointestinal bleeding. The second patient had previously received a live-donor liver at another institution that was lost to chronic rejection. Preoperatively, rHuEPO was used to augment their hemoglobin levels. Intraoperative coagulopathy was managed by the use of aprotinin, desmopressin, and rFVIIa. With the judicious use of ANH and ICS, despite a technically demanding relaparotomy in both instances, hematocrit levels were maintained at 29% at the end of surgery. Both patients recovered uneventfully, had an uncomplicated postoperative course and are well at $2^1/_2$ years follow-up.

Because liver transplantation is traditionally associated with higher blood losses and greater transfusion needs than any other solid organ transplantation, (2) the realization of transfusion-free liver transplantation should facilitate application of these principles with relative ease and safety to other solid organ transplants as well. The Transfusion-Free program at our institution has, using these principles, completed 27 liver transplants (19 live-donor), five live-donor kidney transplants and three heart transplants apart from over 200 other major surgical procedures, with uniformly excellent results (59).

CONCLUSION

Solid organ transplantation has undergone remarkable advancements in recent years and is a glimmer of hope for patients with end-stage organ dysfunction. Transplantation is associated with major hematologic alterations and can

frequently utilize substantial quantities of blood and blood products. The evolving understanding of the unfavorable risk–benefit ratio and major financial and institutional burdens associated with liberal transfusion policies has triggered a search for alternatives to transfusion. An in-depth comprehension and meticulous application of defined principles throughout the perioperative period has been shown to favorably impact blood product utilization. Our own successful experience with the judicious use of principles detailed in this chapter as part of the Transfusion-Free Program at USC serves as a benchmark for its more universal application.

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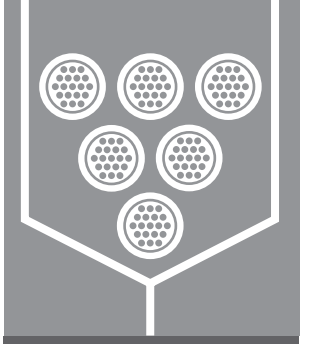

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Blood Use in Orthopedic Surgery

E. Michael Keating *John B. Meding*

Major elective orthopedic surgery is often associated with significant blood loss that can result in acute anemia and the need for allogeneic blood transfusion. Unfortunately, ongoing concerns about the risks associated with allogeneic blood transfusion continue to trouble health care providers despite the advances that have been made in recent years to improve the safety of the blood supply. Even preoperative autologous blood donation, widely used in major elective orthopedic surgeries to reduce the risk of allogeneic blood transfusion, may itself cause or exacerbate anemia in some patients. Nevertheless, it is the potential for significant blood loss in orthopedic surgeries that gives rise to the need for blood conservation strategies.

This potential for significant blood loss is particularly applicable in patients undergoing total hip or knee arthroplasty. In a notably large prospective study, Bierbaum et al. (1) collected data on perioperative blood management practices from a total of 9,482 patients who underwent a total hip replacement (3,920 patients) or total knee replacement (5,562 patients), representing the practices of 330 orthopedic surgeons in the United States. Almost half (46%) of the total population received a blood transfusion (57% in the hip replacement group, 39% in the knee replacement group). Of the patients requiring transfusion, 66% received autologous blood (mean, 1.6 units; range, one to five units) and 34% received allogeneic blood (mean, 2.1 units; range, one to 16 units). The prevalence of breakthrough transfusion, defined as the need for allogeneic blood in patients who had predonated blood, was lowest among patients who had a primary hip (9%) or knee (6%) arthroplasty, and highest in patients who had a revision hip (21%), bilateral knee (16%), or revision knee (11%) arthroplasty. Patients who were transfused with allogeneic blood were more likely to develop an infection ($P \leqslant .001$), experience fluid overload ($P \leqslant .001$), and have increased duration of hospitalization ($P \leqslant .01$) compared with patients who did not receive a transfusion. Similar results were obtained in the prospective Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study of 3,945 patients (2,640 hip arthroplasty and 1,305 knee arthroplasty) from 225 centers in Europe (2). A total of 2,762 (70%) patients received transfusions, including 1,393 (35%) patients who received only autologous transfusions and 1,024 (26%) patients who received only allogeneic transfusions. In the OSTHEO study, allogeneic transfusions were associated with a significantly higher rate (4.2%) of wound infections than autologous transfusions (1%).

Additional studies underscore the high prevalence of allogeneic blood transfusions in total joint replacement surgery. In a recent study of 461 patients who underwent bilateral one-stage total knee arthroplasty (TKA), 98% of patients who did not donate autologous blood required allogeneic blood (3). In this same study, 76% of patients who preoperatively donated one unit of autologous blood required allogeneic blood transfusions, as did 27% of patients who preoperatively donated four units of autologous blood.

Revision TKAs and total hip arthroplasties (THAs) also are associated with significant blood loss and the risk of allogeneic blood transfusion. In 100 patients (52 women, 48 men) who underwent aseptic revision TKA, mean hemoglobin levels decreased 3.1 g per dL and 4.2 g per dL in women and men, respectively, and 19% of women (compared with 4% of men) required allogeneic blood transfusion (4). In 222 patients who had revision THA, the amount of blood reinfused intraoperatively was 356 mL

for those who had revision of the femoral component only, 374 mL for those who had revision of the acetabular component only, and 519 mL for those who had revision of both components (5).

Spinal surgeries can also be associated with significant blood loss. Pediatric patients who undergo posterior spinal fusion surgery to correct scoliosis often require multiple blood transfusions (6). The mean total blood loss reported for 50 consecutive cases of surgical instrumentation and fusion for adolescent idiopathic scoliosis was 1,055 mL (7). Patients in this series with rib resection had a mean blood loss of 1,105 mL, compared with 955 mL in patients not requiring rib resection. The judicious use of blood management agents and techniques can significantly reduce the need for blood transfusions in spinal deformity surgery (8). For example, the risk of requiring allogeneic blood transfusion was only about 7% in one recent study of patients who predonated autologous blood before surgery for scoliosis (9).

Because of the significant blood loss associated with orthopedic surgeries and the risks that accompany allogeneic blood transfusion, the application of a carefully designed blood management program for the orthopedic patient is appropriate. The goals of blood management programs in orthopedic surgery are threefold: to limit blood loss during surgery, to manage perioperative acute anemia, and to reduce the risk of receiving allogeneic blood transfusions. The remainder of this chapter will review the risks associated with allogeneic blood transfusions, indications and guidelines for transfusion, and the host of methods available to the orthopedic surgeon to reduce the need for allogeneic transfusions.

ALLOGENEIC BLOOD TRANSFUSIONS

Marked changes in blood use and collection practices have been noted in the United States over the past several decades. Approximately 10 million red blood cell (RBC) units were transfused in the United States in 1980, rising to a high of 12.2 million units in 1986 and then declining to 11.4 million units in 1997 (10). Similarly, the blood supply in the United States declined from approximately 14 million units in 1986 to 12.5 million units in 1997 (10). Among the factors contributing to this decline are the loss of donors because of enhanced screening and testing procedures and the misconception by some potential donors that human immunodeficiency virus (HIV) can be transmitted by the process of blood donation. Although the blood supply is declining, substantial demands are anticipated in the future with a predicted doubling of the proportion of the U.S. population that is over 65 years of age by the year 2030. Public perception of the risk of blood transfusion is also a concern. In a national telephone survey of 1,204 people conducted in the United States between 1997 and 1998, a substantial proportion of respondents did not consider the blood supply to be safe and said they would not accept banked blood if they were hospitalized (11).

Although the general public has expressed concern about the safety of the blood supply and, in particular, the risk of HIV transmission via blood transfusion, (11) the estimated risk of disease transmission via transfusion is lower than ever before and the blood supply in the United States and other developed countries has never been safer (10,12). After the introduction of nucleic acid technology to screen donor blood, estimates of per unit risks of transmission are 1 in 1,800,000 for HIV and 1 in 1,600,000 for hepatitis C (12). Nevertheless, transfusion of allogeneic blood is not without risk (Table 41.1) (10,12–14). At present, the most serious known risks from blood transfusion are hemolytic reactions from ABO-incompatible blood transfusion caused by administrative error, transfusion-related acute lung injury, and bacterial contamination in platelet products (13). It is also known that exposure to leukocytes in allogeneic blood and subsequent sensitization can cause an immunosuppressive effect (10). However, the clinical importance of this immunosuppression remains to be clearly defined. Interestingly, there is some evidence to suggest that allogeneic blood transfusion may increase the risk of infection after orthopedic surgery. In a study of 1,206 patients who underwent primary THA between 1990 and 1995, the incidence of postoperative infection was 8.4% in patients receiving no transfusion and 14% in those receiving allogeneic transfusion ($P = .035$) (14).

TABLE 41.1
RISKS ASSOCIATED WITH ALLOGENEIC BLOOD TRANSFUSION

Risk	Comment
Viral transmission (12)	HIV: Risk of 1 in 1,800,000 units transfused HCV: Risk of 1 in 1,600,000 units transfused
ABO-incompatibility reaction (13)	Most often caused by administrative error
Transfusion-related acute lung injury (13)	Characterized by acute respiratory distress and pulmonary edema
Bacterial contamination (13)	Primarily occurs in platelet products
Immunosuppression (10)	Exposure to leukocytes leads to sensitization
Infection (postoperative) (14)	May be related to immunosuppression

HIV, Human immunodeficiency virus; HCV, Hepatitis C virus.

Because of ongoing concerns about the risks associated with allogeneic blood transfusions, health care providers have sought to implement blood conservation strategies that take advantage of safe and effective alternatives to transfusion. Appropriate use of these alternatives requires careful preoperative planning, including the implementation of practice standards and guidelines.

Indications and Guidelines for Transfusion

If exposure to allogeneic blood is to be reduced, comprehensive blood conservation programs must be developed and implemented. This is best accomplished through the establishment of evidence-based guidelines that identify which patients might benefit most from various blood conservation techniques and that consider both resource implications and cost effectiveness.

General guidelines for blood transfusion have been issued by a number of organizations including the American College of Physicians, (15) the Canadian Medical Association, (16) and the National Institutes of Health (17). These guidelines do not recommend prophylactic transfusion and define a hemoglobin (Hb) level of 7.0 to 8.0 g per dL as an appropriate transfusion trigger for patients who are not critically ill (10). Although compliance with blood conservation guidelines for elective orthopedic surgery has been reported to be low, (18) implementation can be enhanced if the guidelines do not require major institutional changes and are characterized by simplicity, wide distribution, endorsement by local opinion leaders, and development of a sense of ownership by clinicians (19).

Studies have shown that estimated perioperative blood loss and preoperative Hb concentration are significant predictors of the need for blood transfusions (20,21). Bierbaum et al. (1) demonstrated that the lower the baseline Hb level, the greater the probability of allogeneic blood transfusion in patients undergoing THA or TKA. Of the 3,020 patients who had a baseline Hb of £13.0 g per dL, 864 (29%) required a transfusion of allogeneic blood. More recently, a retrospective study of 296 patients who underwent THA or TKA documented a significant ($P = .0001$) relationship between the need for postoperative transfusion and the preoperative Hb level (22). In this retrospective study, patients with a preoperative Hb <13.0 g per dL had a four times greater risk of transfusion than did those with Hb levels between 13.0 and 15.0 g per dL. Although the transfusion threshold of Hb 10 g per dL and HCT 30% (the 10/30 rule) is no longer accepted, investigations of lower transfusion thresholds have not determined an optimal transfusion threshold for all patients (23). Instead, the decision for blood transfusion should be based on the individual patient's overall clinical status and the nature of the anemia (e.g., acute versus chronic) when other measures of RBC repletion have failed (24).

METHODS TO REDUCE ALLOGENEIC TRANSFUSIONS

Cost management pressures over the last decade and continued public concern about the safety of the blood supply have precipitated a concerted effort among orthopedic surgeons and other surgical specialties to refine existing blood conservation measures and to develop new approaches. The blood management options currently available to orthopedic surgeons include reduction of intraoperative blood loss and use of blood retrieval and augmentation strategies. These strategies encompass such methods as refinement of preoperative protocol and surgical techniques, preoperative and operative pharmacologic interventions, preoperative autologous donation (PAD), acute normovolemic hemodilution (ANH), intraoperative and postoperative RBC retrieval and reinfusion, and recombinant human erythropoietin (Table 41.2). These blood conservation strategies are reviewed below.

Surgical Technique

Surgeons can minimize blood loss and maintain operative hemostasis through careful adherence to prescribed guidelines and by employing, as appropriate, operative techniques known to reduce blood loss safely and effectively, such as electrocautery and argon-beam coagulation.

Although minimally invasive surgical techniques have been introduced for both THA (25) and TKA, (26) there is a lack of published data on blood loss and the associated need for allogeneic blood transfusion with these techniques. Although one surgeon reported a mean blood loss of 200 mL for minimally invasive TKA compared with his historically based blood loss of 350 to 400 mL for standard-incision TKA, this was not a rigorously controlled comparison (27).

The application of hypotensive anesthesia has also shown promise as an option for blood management in the orthopedic setting. In an early study of patients undergoing primary THA with epidural anesthesia, a difference in mean arterial blood pressure of 10 mm Hg, from 60 mm Hg to 50 mm Hg, significantly ($P = .004$) reduced mean blood loss from 263 mL to 179 mL (28). More recent studies have demonstrated statistically significant reductions in blood loss for both THA (29) and TKA (30) using the technique of hypotensive epidural anesthesia.

Perioperative Pharmacologic Interventions

Pharmacologic agents available to the orthopedic surgeon or under investigation for the maintenance of perioperative

TABLE 41.2
BLOOD CONSERVATION OPTIONS IN ORTHOPEDIC SURGERY

Categories	Blood Management Options
Transfusion practice standards	Lowering the transfusion trigger
Surgical techniques	Operative technique
	Minimally invasive surgery
	Electrocautery (argon-beam coagulation)
	Hypotensive anesthesia
Perioperative pharmacologic interventions	Locally active agents (thrombin, collagen, fibrin glue)
	Antifibrinolytics (aprotinin, tranexamic acid)
	Oxygen transport agents (PFC and HBOC)
Autologous blood donation	Preoperative autologous blood donation (PAD)
	Acute normovolemic hemodilution (ANH)
	Blood salvage (intraoperative/postoperative)
Preoperative pharmacologic augmentation therapies	Recombinant human erythropoietin

HBOC, Hemoglobin-based oxygen carrier; PFC, Perfluorocarbon emulsions.

hemostasis include topically active agents and the antifibrinolytics (24). It is important to note that these agents are distinct from preoperative pharmacologic augmentation therapies, such as epoetin alfa, that directly treat anemia.

Topically or locally active agents include thrombin, collagen, and fibrin glue. In a study of 53 patients undergoing unilateral primary TKA, the use of a fibrin sealant was shown to reduce the mean postoperative blood loss from 408 mL in the control group to 184 mL ($P = .002$) in the treatment group (31). The fibrin sealant was sprayed onto the wound before tourniquet deflation and wound closure.

Antifibrinolytic drugs are increasingly being used to maintain perioperative hemostasis, despite earlier concerns about high cost and the risk of thromboembolic complications (32). Antifibrinolytic agents with promise for application in orthopedic surgeries include aprotinin and tranexamic acid. In an early study of 40 patients undergoing primary THA, aprotinin was shown to reduce blood loss from 1,943 mL in the control group to 1,446 mL ($P < .05$) in the treatment group, and mean blood transfusions from 3.4 units in the control group to 1.8 units ($P < .001$) in the treatment group (33). These promising early results with aprotinin are supported by more recent studies. In patients admitted for major orthopedic surgery (revision arthroplasty of the hip or knee, or resection of soft-tissue sarcoma), treatment with aprotinin reduced mean blood loss from 1,957 mL in the control group to 736 mL ($P = .002$) in the treatment group, and mean blood transfusions from 3.1 units in the control group to 1.4 units (34). Aprotinin has also recently been shown to reduce blood loss (aprotinin, 545 mL; placebo, 930 mL) and transfusion requirements (aprotinin, 1.1 units; placebo, 2.2 units) during posterior spinal fusion surgery in 44 children (35). Similarly, tranexamic acid has been shown to reduce the need for allogeneic blood transfusions in major orthopedic surgery. In a meta-analysis of 12 clinical trials, intravenous tranexamic acid reduced the proportion of patients requiring allogeneic blood transfusion, total amount of blood loss, and total number of allogeneic blood units transfused compared with placebo (36). The positive results from this meta-analysis were supported by a recent prospective randomized double-blind trial of 40 patients undergoing primary unilateral THA (37). In this prospective study, fewer patients in the tranexamic acid group required allogeneic RBC transfusion ($P = .0012$), with a lower median number of transfused units per patient compared with placebo ($P = .03$).

Two groups of oxygen-transport agents—perfluorocarbon (PFC) emulsions and hemoglobin-based oxygen carriers (HBOCs)—are in clinical development to enhance the oxygen-delivery capability of blood and reduce the need for allogeneic transfusion (38). Perfluorocarbons are synthetic fluorinated hydrocarbons that increase dissolved oxygen in the fluid phase of blood without binding the oxygen molecule. Fluosol, a PFC, was approved in 1989 as an adjunct for oxygen delivery during angioplasty procedures; however, with improvements in mechanical means of maintaining blood flow during angioplasty, Fluosol became obsolete and was removed from the U.S. market in 1994. Although several second-generation PFC emulsions are undergoing clinical development and show some promise, none are currently marketed in the United States (38). Hemoglobin-based oxygen carriers are either cross-linked or microencapsulated hemoglobin molecules that can be sterilized by pasteurization or ultrafiltration, virtually eliminating the risk of bacterial or viral disease transmission. Modification

of hemoglobin by cross-linking eliminates the risk of renal toxicity and improves the oxygen dissociation characteristics of the molecules. Several HBOCs have been tested in phase III clinical trials but none have yet been approved for market.

Preoperative Autologous Blood Donation

Preoperative autologous blood donation is commonly performed before major elective orthopedic surgeries to meet potential perioperative transfusion needs. However, there is some evidence to suggest that the use of PAD may be declining. In a survey of patients participating in a PAD program in Canada between 1993 and 2000, autologous donations have declined by 26% after peaking in 1995 (39). For TKA, THA, and scoliosis, utilization rates were 60%, 83%, and 78%, respectively, in 1993 compared with 50%, 58%, and 58%, respectively, in 2000. This declining use may be related to the rising awareness of reports of risks associated with PAD, such as anemia, ischemic events, and adverse events severe enough to require hospitalization (40–43). Further more, the magnitude of compensatory erythropoiesis to replace donated red blood cells has generally been overestimated (44). The frequent overcollection and resulting wastage of blood is another limitation of PAD. Because of the risks of anemia and costs associated with overcollection, it is important for clinicians to be selective when considering PAD for elective surgeries. The possibility of human error in the administration of predonated blood should also be considered. Moreover, a recent systematic review of 68 randomized trials and 81 controlled observational studies showed that PAD decreased allogeneic transfusion rated by 63% (95% CI = 46% to 74%) but increased overall transfusion rates by 30% (95% CI = 12% to 48%) and reduced preoperative mean Hb levels by 1.23 g per dL (45).

Guidelines for the appropriate use of PAD have been published which recommend that patients be stratified according to the risk of requiring transfusion on the basis of preoperative Hb levels and the estimated blood loss associated with the scheduled procedure (46). Preoperative Hb levels are readily attained, and therefore offer a practical approach to estimating transfusion risk. Algorithms have been developed that determine low and high risk for transfusion on the basis of estimated blood loss and preoperative HCT, but they may have limited usefulness because of difficulty in predicting actual blood loss for any given procedure or individual patient. In addition to risk assessment and evaluation of overall health status, patients being considered for PAD should receive supplemental oral iron therapy (e.g., ferrous sulfate 325 mg, three times a day) and other dietary supplements. Autologous blood donation should then begin 3 to 5 weeks before the scheduled surgery date.

Recent reports have questioned the usefulness of PAD in TKA and THA. A standard PAD policy with liberal transfusion criteria was compared with a more restrictive policy with transfusion based on individual patient factors; no increase in the rate of allogeneic transfusions was associated with the more restrictive policy (47). Similarly, PAD did not show benefit over postoperative blood salvage in reducing the risk of allogeneic transfusion in patients undergoing TKA (48,49). Because of these documented limitations in PAD, perioperative blood salvage has been proposed as an alternative to PAD for primary TKA and THA (50).

In summary, PAD allows patients to fulfill blood requirements for planned surgical procedures with minimal risk of transfusion-transmitted diseases. However, PAD is not without risk, is sometimes wasteful, may be of limited usefulness, and should be used judiciously only after careful preoperative planning.

Acute Normovolemic Hemodilution

Considered an alternative to PAD, acute normovolemic hemodilution (ANH) involves removal of whole blood from a patient immediately before surgery and simultaneous replacement with acellular fluids, such as crystalloid and colloid, to maintain normovolemia (44). The blood is collected in an anticoagulant-containing bag and stored in the operating room, available for reinfusion after any major loss of blood. Guidelines for ANH recommend that this approach be considered when the potential surgical blood loss is likely to exceed 20% of blood volume in patients who have a preoperative Hb level >11 g per dL (51).

In contrast with banked blood, ANH does not require testing to screen for transfusion-transmitted viral diseases, and therefore results in reduced costs. Furthermore, there is virtually no risk of bacterial contamination or of an administrative error that could lead to an ABO-incompatible blood transfusion. In addition, ANH does not require the additional time investment from patients to donate blood before the surgery, nor does it prolong duration of surgery and anesthesia (52). However, ANH is contraindicated in patients who have coronary artery disease or renal, pulmonary, or severe hepatic disease (24). Furthermore, because the precision required to implement the technique is time-consuming, the use of ANH is often impractical in many orthopedic procedures that are of short duration (24). Finally, a recent meta-analysis of 42 clinical trials comparing ANH with usual care or another blood conservation method concluded that the literature supports only modest benefits from ANH and, because the safety of the procedure is unproven, widespread use of ANH cannot be encouraged (53).

Intraoperative RBC Retrieval and Reinfusion

Intraoperative blood recovery involves the collection and reinfusion of autologous blood lost by the patient during surgery. Because there is no storage of blood, this method provides the convenience of immediate availability in the event of rapid blood loss, although specialized equipment and personnel are needed. Cell-washing devices can provide the equivalent of 10 units of banked blood per hour to a patient with massive bleeding (44). Because cell-washing devices do not completely remove bacteria from recovered blood, this technique should not be used if the operative field has gross bacterial contamination (51). Contraindications to the use of intraoperative blood recovery include the potential for aspiration of malignant cells, the presence of infection, or the presence of contaminants such as amniotic or ascitic fluid. Furthermore, there have been rare reports of deaths (estimated risk of 1 death in 35,000 procedures) related to intraoperative blood recovery (44). There is also the question of whether intraoperative blood recovery reduces the need for blood transfusions. Studies in patients undergoing cardiothoracic surgery (54) or surgical repair of abdominal aortic aneurysms (55) showed that intraoperative blood recovery resulted in little or no reduction in the need for blood transfusions. Nevertheless, the intraoperative recovery of blood may still be of value in patients with substantial blood loss during surgery because it provides blood that is less costly to obtain and is immediately available in the event of rapid blood loss (44).

Postoperative Collection and Reinfusion

Postoperative blood recovery involves the collection of blood from surgical drains followed by reinfusion, with or without processing. Because unprocessed recovered blood is partially hemolyzed, defibrinated, and likely to contain cytokines, there usually is a threshold for the volume of unprocessed blood that can be reinfused. This technique has most commonly been used after cardiac surgery (44). However, the value of postoperative blood recovery in this patient population is controversial, with some evidence showing a benefit (56) and other evidence showing a lack of efficacy (57).

The safety and usefulness of postoperative blood recovery after orthopedic surgery also remains controversial (58,59). A study in 232 patients who underwent THA demonstrated that blood salvage after surgery decreased the need for transfusion and was not associated with any complications (60). If a surgical drain is not placed, however, the technique cannot be used. Furthermore, increased interleukin-6 concentrations in shed drainage blood after TKA have been associated with febrile reactions after retransfusion, (61) and reinfusion of unwashed drainage blood following THA induced an activation of the plasma coagulation pathway with renewed clot formation and fibrinolysis in patients (62). Because of the high cost and questionable benefit–risk ratio of this technique, postoperative blood recovery should be limited to cases in which large postoperative blood losses are anticipated, such as in bilateral joint-replacement surgery (44).

Recombinant Human Erythropoietin (Epoetin Alfa)

Erythropoietin is a glycoprotein hormone synthesized in the kidney and secreted by renal cortical interstitial cells in response to tissue hypoxia. It is the main regulator of erythropoiesis (Fig. 41.1) (63). As such, it functions in the differentiation and production of erythroid progenitor

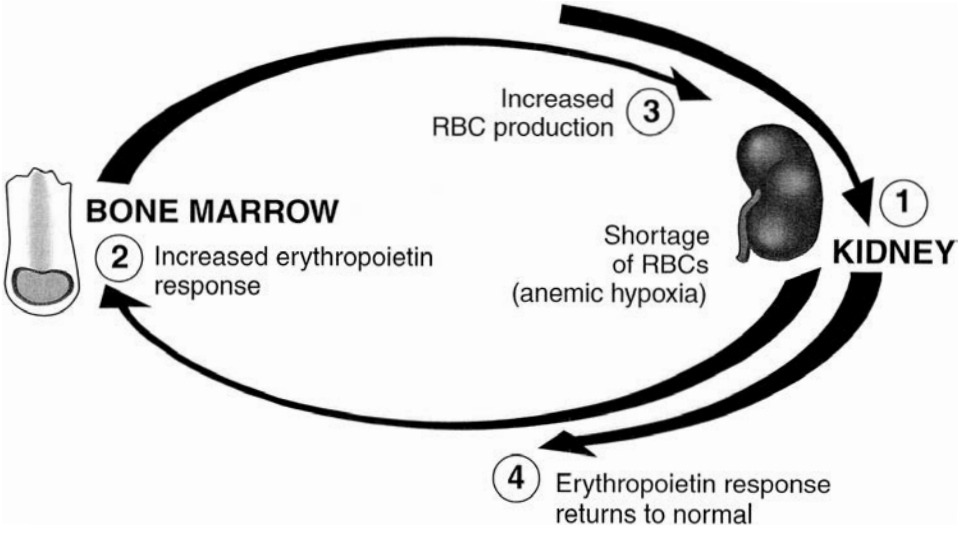

Figure 41.1 Regulation of erythropoietin synthesis. **A:** Erythropoietin is synthesized predominantly in the kidney in response to tissue hypoxia. **B:** Erythropoietin stimulates the proliferation and differentiation of RBC precursors in the bone marrow. **C:** The resulting increase in RBC production improves tissue oxygenation. **D:** Erythropoietin levels decrease to baseline as the feedback loop is completed. Reproduced with permission from Bieber E. Erythropoietin, the biology of erythropoiesis and epoetin alfa. An overview. *J Reprod Med*. 2001;46(suppl):521–530.

cells and stimulates the synthesis of hemoglobin. Epoetin alfa is a genetically engineered molecule that is identical to erythropoietin in its amino acid sequence and biologic activity (64). Epoetin alfa has been available for more than 10 years and, like endogenous erythropoietin, safely and effectively stimulates erythropoiesis. Epoetin alfa has been used to treat anemia in patients with chronic renal failure, nonmyeloid malignancies, and HIV infection. It has also been used perioperatively in orthopedic patients. The preferred route of administration of epoetin alfa is subcutaneous because this route provides sustained plasma levels and a long half-life (65).

Epoetin alfa has been shown to be effective in the perioperative treatment of anemia in patients undergoing orthopedic surgery (65). It was initially used to help improve the success of autologous donation (64). A subsequent study showed that patients undergoing elective orthopedic surgery who were treated with epoetin alfa 300 IU/ kg/day for 15 days perioperatively were significantly ($P < .001$) less likely to require a blood transfusion (17%) compared with patients who received placebo (54%) (66). The transfusion risk was greatest in patients who had a prestudy Hb of between 10 and 13 g per dL (78%) compared with patients who had a prestudy Hb >13 g per dL (36%) (66). Later studies showed that two different treatment regimens of epoetin alfa (300 IU/kg/day for 15 days perioperatively or 600 IU per kg in 4 weekly doses beginning 21 days before surgery) were safe and effective in the treatment of perioperative anemia in orthopedic patients with a preoperative Hb between 10 and 13 g per dL (67–69). Both treatment regimens increased preoperative Hb concentrations and reduced the need for allogeneic transfusions in patients with perioperative anemia. Allogeneic transfusions were required by 20% of patients in the epoetin alfa 300 IU per kg daily group and by 16% of patients in the 600 IU per kg weekly group (69). Not only has the weekly dosage regimen been shown to be equally as effective as the daily regimen, it also decreases the total dose by almost half (from 4,500 to 2,400 IU per kg), which can have a significant economic impact on the cost of drug treatment (69). Summary results for the reduction of transfusion incidence from the three pivotal clinical trials of epoetin alfa are presented in Figure 41.2 (66–68,70).

It is important to note that iron is a rate-limiting factor for erythropoiesis, and iron deficiency may develop in anemic patients receiving epoetin alfa treatment if adequate iron stores are not available. Therefore, epoetin alfa should be administered concomitantly with supplemental iron (71). Studies have demonstrated that epoetin alfa was effective with either daily oral iron supplements for 2 weeks or weekly IV iron administration for 2 weeks and that iron alone was not sufficient for stimulating RBC production (72,73).

The safety and efficacy of the epoetin alfa weekly regimen was compared with those of PAD in a study of 490 patients undergoing TKA or THA (74). A smaller proportion (12.9%) of patients in the epoetin alfa group required allogeneic

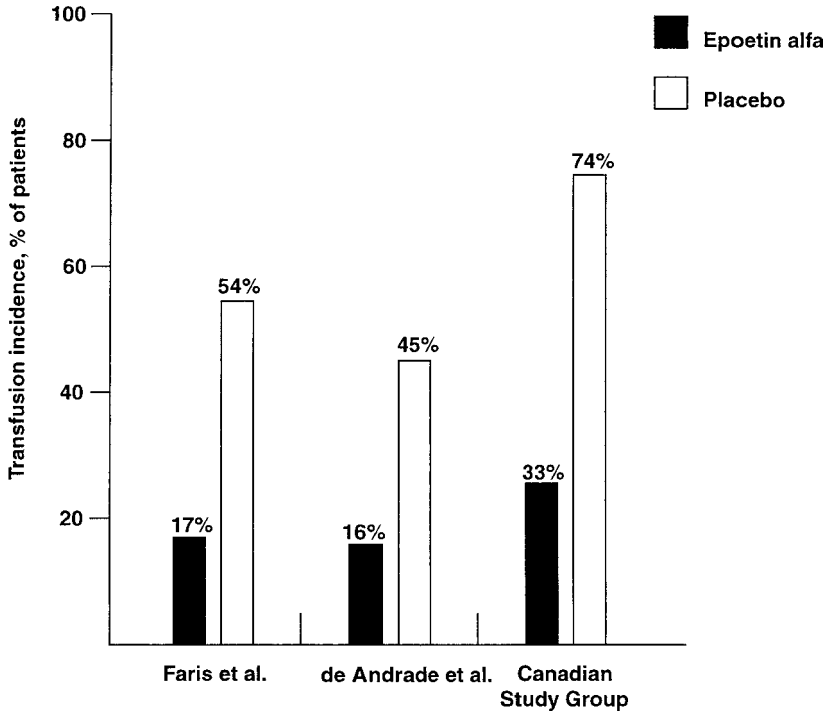

Figure 41.2 Epoetin alfa treatment (300 IU per kg) and incidence of blood transfusions in three pivotal studies. Data from Faris PM, Ritter MA, Abels RI. The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. The American Erythropoietin Study Group. J Bone Joint Surg Am. 1996;78:62–72;de Andrade JR, Jove M, Landon G, et al. Baseline hemoglobin as a predictor of risk of transfusion and response to Epoetin alfa in orthopedic surgery patients. Am J Orthop. 1996;25:533–542; Canadian Orthopedic Perioperative Erythropoietin Study Group. Effectiveness of perioperative recombinant human erythropoietin in elective hip replacement. Lancet. 1993;341:1227–1232; Stovall TG. Clinical experience with epoetin alfa in the management of hemoglobin levels in orthopedic surgery and cancer. Implications for use in gynecologic surgery. J Reprod Med. 2001;46(suppl):531–538.

transfusion compared with the proportion in the PAD group (19.2%), although this difference was not statistically significant ($P = .078$). Furthermore, the epoetin alfa group had significantly ($P < .0001$) higher mean Hb levels preoperatively and postoperatively on day 1 and at discharge.

Nevertheless, PAD has long been considered a gold standard for decreasing the risk of allogeneic transfusion in orthopedic surgery and in several states is even required by law to be offered to patients (1,75,76). Initially, PAD was thought to be less costly on a per patient basis than treatment with epoetin alfa; however, unless used judiciously, a significant amount of predonated autologous blood is wasted, thus increasing the total cost of PAD. For example, Bierbaum et al. (1) reported that in their study of 9,482 patients who underwent THA or TKA, almost half (45%) of predonated blood units were not used. Unilateral primary TKA and revision TKA were associated with the highest percentages of wasted units (55% and 47%, respectively), whereas bilateral TKA and revision THA were associated with the lowest percentages (29% and 30%, respectively). Notably, 42% of the patients in this study who predonated blood did not require a transfusion.

Numerous studies have demonstrated the safety and effectiveness of epoetin alfa in the orthopedic surgery population. However, epoetin alfa, despite its safety and effectiveness, has been considered inconvenient to use because patients are required to return for a dose at 21 days, 14 days, and 7 days before surgery (1,75,76). Adding to this perception of inconvenience, some Medicare carriers approved epoetin alfa for use in patients undergoing elective surgery, whereas others have limited its use to hip and knee surgery only. Each Medicare carrier has its own requirements for payment. These requirements include that the operation be expected to result in the loss of >2 units of blood; preoperative Hb level must be between 10 and 13 g per dL; and the patient must be unwilling or unable to donate autologous blood (77). Some carriers have also requested that the diagnosis of the patient's anemia be due to chronic disease. This restrictive language has been included in the Medicare reimbursement policy and has indeed been an impediment to the use of epoetin alfa because it is easier to order PAD than to satisfy the requirements for Medicare reimbursement.

However, recent studies continue to question the efficacy of PAD in orthopedic surgery, suggesting that alternatives such as epoetin alfa warrant ongoing consideration. For example, a recent study comparing PAD with iron therapy in THA showed no difference in risk for allogeneic transfusion between the two groups (75). The authors concluded that PAD actually increased the likelihood of autologous transfusion, resulted in waste of predonated units, and increased costs.

The debate over the relative utility of PAD is also compounded by the growing general acceptance of a lower transfusion trigger to an Hb level of 7 or 8 g per dL. Lower transfusion triggers increase the likelihood of wastage of predonated autologous blood units. In a large retrospective cohort study of 8,787 patients ⩾60 years of age with hip fractures who underwent surgical repair, perioperative transfusion in patients with Hb levels ⩾8 g per dL did not appear to influence the risk of 30-day or 90-day mortality (78). However, in another study of patients with hip fractures, transfusion of allogeneic blood was shown to increase the risk of serious bacterial infection by 35% and pneumonia by 52%, further supporting the use of a lower transfusion trigger to minimize transfusions (79).

Hospital managers are increasingly sensitive to the costs associated with PAD programs and transfusion protocols, particularly to those costs associated with the acquisition, storage, and processing of wasted units. The potential for reducing or eliminating the costs associated with the wasting of autologous blood units has prompted some hospitals to initiate and administer an epoetin alfa program that satisfies the requirements for Medicare reimbursement. These programs offer potential in light of published data, which show that the decreases in mean Hb in THA and primary unilateral TKA are 4.07 g per dL (± 1.7 g per dL) and 3.85 g per dL (± 1.4 g per dL), respectively (65,80). Assuming these decreases in mean Hb for THA and TKA and a transfusion threshold of 8.0 g per dL, those patients with Hb levels between 5.2 to 5.8 g per dL above the predicted transfusion threshold will have an approximately 17% risk of receiving an allogeneic blood transfusion. For most patients, this equates to a preoperative Hb level >13 g per dL. Therefore, it is reasonable to expect that epoetin alfa-induced increases in preoperative Hb level >13 g per dL could lead to a significant decrease in allogeneic blood transfusion risk without the use of autologous blood or other conservation techniques.

Another potentially useful application of epoetin alfa in orthopedics is in the two-stage treatment for total joint infections. It is well documented that patients with prolonged joint sepsis have anemia of chronic disease (81). It is also well documented that transfusion of allogeneic blood can increase perioperative infection rates (1) and down regulate host macrophage and T-cell immunity (82,83). Therefore, the prevention of recurrent infection should be enhanced by the avoidance of allogeneic transfusions. Recently, studies have shown that treating patients with epoetin alfa between the two stages of excisional arthroplasty and reimplantation can decrease the allogeneic transfusion rate in both THA and TKA. In THA, the proportion of patients exposed to allogeneic blood transfusions after reimplantation was reduced from 87% in the control group to 47% in the epoetin alfa group ($P < .01$) (84). Similarly,

the risk of allogeneic transfusion during reimplantation in two-stage TKA for infection was reduced from 83% in the control group to 34% in the epoetin alfa group (85). These studies, although small, identify a use of epoetin alfa that has great potential to improve outcomes in orthopedic surgery.

SUMMARY

The primary goal of blood management in orthopedic surgery is to reduce or eliminate the need for allogeneic blood transfusion. Continuing efforts to achieve this goal have led to notable advances in existing blood conservation strategies and to the development of new approaches. These efforts have included the development of transfusion practice standards, improvements in surgical practice, and the judicious use of hemostatic agents, perioperative blood salvage, PAD, and epoetin alfa. Despite these advances, there is a continuing need for better awareness in the medical community about the pros and cons of each strategy, including issues of cost. Exploration into further refinements in the development and application of blood conservation strategies is warranted.

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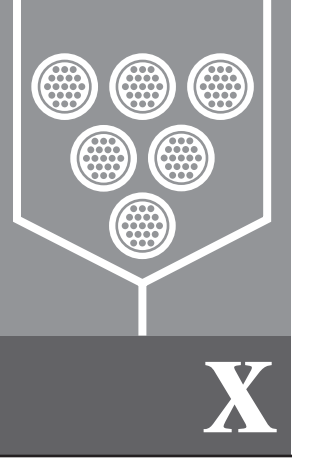
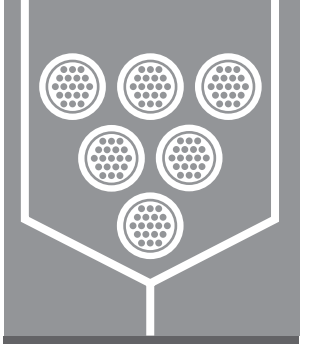


Transfusion Issues in Other Specialties



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Blood Management in Obstetrics and Gynecology

Arnold J. Friedman

Modern blood management generally recognizes the importance of blood conservation, both from the perspective of the patient, who benefits from the avoidance of unnecessary transfusion, and society, which benefits from the appropriate consumption of a limited resource. Most of the blood-related scientific information, pharmacologic agents, and surgical and anesthetic techniques important for blood management in other fields of medicine can be applied equally to the gynecologic patient. The pregnant woman, on the other hand, by virtue of her anatomy and physiology and those of the fetus she carries, presents unique challenges to her caregivers. This chapter will focus on the pregnant woman as blood management relates to her.

OBSTETRICS

Any discussion of blood management in obstetrics is by its nature about obstetrical hemorrhage. Hemorrhage is the cause of nearly 30% of maternal deaths in the United States (1) and of the 500,000 pregnancy-related deaths worldwide (2). When hemorrhage occurs it can be sudden, severe, unanticipated, and catastrophic. The goal in caring for these women is to obtain a healthy outcome with minimal morbidity for mother and baby, while minimizing the use of allogeneic blood products. This chapter will provide guidelines for doing so.

COMPENSATORY PHYSIOLOGIC ALTERATIONS OF PREGNANCY

Uterine bleeding at the time of delivery is a normal and expected occurrence. Although accurate measurement of blood loss at delivery is difficult, most experts accept as normal 500 mL for a vaginal delivery and 1,000 mL for cesarean delivery (3). Several physiologic changes occur during pregnancy to accommodate this anticipated blood loss.

During the first half of pregnancy there is a 30% to 40% increase in intravascular volume. At the same time, there occurs a 20% to 30% increase in red cell mass. The result of these increases is a net hemodilution reflected in a physiologic drop in hematocrit commonly referred to as the *physiologic anemia of pregnancy*. The total increase in blood volume and red cell mass is sufficient to compensate for the normal expected bleeding that occurs at delivery.

In addition to these alterations in blood volume and red cell concentration, mechanisms exist to minimize blood loss at the time of childbirth. Immediately after delivery, the uterus rapidly contracts resulting in a dramatic decrease in its internal surface area. This contraction aids in separation of the placenta and occlusion of the myometrial blood vessels that had been supplying the placenta. The rapid contraction of the uterus also results in a significant autotransfusion of maternal blood previously sequestered within the uterine walls.

Finally, pregnancy is a hypercoagulable state, with clotting factors and function at their maximum immediately following delivery and extending about 30 days into the postpartum period. These coagulation changes further minimize bleeding from both vaginal and cesarean delivery. Despite these mechanisms, between 1.3% and 2.6% of deliveries are associated with red cell transfusion (4,5).

POSTPARTUM HEMORRHAGE

For many reasons estimates of blood loss at the time of delivery are highly subjective and generally thought to be 30% to 50% lower than actual. As a result, postpartum hemorrhage may be difficult to diagnose immediately. One accepted definition is a hematocrit drop of 10 points from before to after delivery, (3) but of course, this is a retrospective finding. Using this definition, approximately 4% of vaginal (6) and 6% of cesarean (7) births are complicated by hemorrhage. In order to maximize patient outcome while minimizing blood loss and blood product requirement, the physician must address hemorrhage proactively. This can be accomplished through a three-step approach analogous to that described by Shander et al. (8) in their discussion of perioperative blood conservation:

1. Optimize the patient's reserve.
2. Control blood loss at the time of delivery.
3. Conserve autologous blood.

OPTIMIZING RESERVE

The Patient at Risk

Modern blood management in obstetrics begins long before delivery. Although the obstetrician must be prepared for hemorrhage in every pregnancy, some pregnancies deserve a heightened level of concern. Identifying these high risk women in advance should allow for better preparation and an opportunity to reduce morbidity.

Numerous risk factors for postpartum hemorrhage can be elicited from the patient's history (9,10). A previous episode of postpartum hemorrhage significantly increases future risk. A history of prior coagulation disorder, platelet abnormality, aspirin, or anticoagulant use or unexplained bleeding needs to be evaluated and corrected if possible. Specific obstetrical conditions such as grand multiparity, prior vertical uterine incision, and previous cesarean section all add significant risk of excessive bleeding for the current pregnancy.

Certain findings in the current pregnancy should raise concerns about bleeding at delivery (9,10). Among these are conditions that overdistend the uterus such as fetal macrosomia, multiple gestation, and polyhydramnios. Abnormal placentation, such as placenta previa and placenta accreta, is a major risk factor. Many of these conditions can be diagnosed on routine ultrasound examination (11). The finding of two or more risk factors in a woman undergoing cesarean section dramatically increases the risk. For example, the history of one prior cesarean delivery combined with ultrasound diagnosis of placenta previa is associated with a 25% chance of placenta accreta, and two prior cesareans raises the risk to 40% (12). Magnetic resonance imaging may be valuable in confirming the diagnosis. When possible, these high risk pregnancies should be delivered prior to bleeding, as early as fetal maturity will allow. The ability to perform a planned delivery during daylight hours can make a huge difference in blood loss and the availability of treatment resources.

Peripartum events may also greatly increase the risk of hemorrhage. Tocolysis for preterm labor, pre-eclampsia, chorioamnionitis, and prolonged labor all increase the risk of postpartum uterine atony and hemorrhage at the time of delivery. Placental abruption, instrumental delivery, and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome should raise the level of concern dramatically.

Anemia in Pregnancy

Because of the physiologic hemodilution and despite the increased red blood cell mass of pregnancy most pregnant women have lower than normal nonpregnant hematocrits. In pregnancy, therefore, a *normal* hemoglobin level is generally accepted as 10.5 g per dL in the second trimester when hemodilution is greatest, and 11 g per dL in the first and third. Between 20% and 40% of pregnant women are anemic (13). Although the great majority of these women are iron deficient, the exact prevalence of iron deficiency is uncertain. Anemia in pregnancy has been associated with preterm birth, low birth weight, and other adverse outcomes (13) including an increased rate of maternal transfusion (14–16). Because of the high prevalence of anemia and iron deficiency, the U.S. Preventive Services Task Force recommends routine oral iron supplementation for all pregnant women (13). Bayoumeu et al. (17) studied the relative efficacy of oral iron therapy in 50 late second trimester anemic women (Hb level between 8 and 10 g per dL). After 30 days of treatment they found a rise in hemoglobin level equivalent to that in the group treated intravenously, though iron stores as measured by ferritin levels were significantly higher in the intravenous group. The authors point out the possibility that had the intravenous group been treated with more aggressive dosing, their hemoglobin rise might have occurred faster. In any case, this study confirms the efficacy of oral supplements in compliant patients. However, because

many women cannot tolerate oral iron without gastrointestinal side effects, only 70% are thought to be compliant. For these women and others at high risk, intravenous iron replacement should be a consideration.

Until recently iron dextran was the only parenteral preparation available in the United States for intravenous use. Its use was somewhat restricted because of reports of a 1% risk of anaphylactoid reactions. However, over the past few years, two new preparations have become available. Sodium ferric gluconate complex (Ferrlecit) and iron sucrose (Venofer) are both associated with a much lower risk of these complications and the latter has been used safely in pregnancy. It is thought that the lower rate of intolerance of iron sucrose is partly due to the low allergenicity of the sucrose complex and partly due to the slow release of elementary iron from the complex. Accumulation of iron sucrose complex in organ parenchyma is low compared to iron dextran and iron gluconate, and incorporation into the bone marrow for erythropoiesis is faster (18). Intravenous iron therapy has been proven effective both as first line treatment and as followup to failed oral iron therapy (19).

The third component of the treatment of iron-deficiency anemia is recombinant human erythropoietin (rHuEPO). Its use in pregnancy was quite limited until recently because of concerns about its safety and efficacy for the pregnant woman and fetus. Current information strongly suggests that erythropoietin does not cross the placenta (20) and that fetal erythropoiesis is independent of maternal erythropoietin level. There is therefore no direct risk of rHuEPO to the fetus. Once fetal safety had been established, researchers began using the drug successfully to treat pregnant women with anemia related to renal disease (21–24). Ultimately, numerous small studies of pregnant anemic women without renal disease have appeared documenting the efficacy and safety of rHuEPO in pregnancy (25–27). Despite the already elevated levels of erythropoietin in pregnant women (two to four times nonpregnant levels, (28,29) rHuEPO is effective in raising hemoglobin levels in anemic pregnant patients. Sifakis et al. (27) studied 26 pregnant women with iron deficiency anemia (Hb $<$ 8.5 g per dL) unresponsive to oral iron. After 2 weeks treatment with rHuEPO and intravenous iron, 73% had normal hemoglobin levels. Yet the ideal role and dosage of rHuEPO in this population have yet to be established. Breymann et al. (19) reported in 2001 on the relative efficacy of intravenous iron versus intravenous iron plus rHuEPO in treating pregnant anemic women who had already failed to respond to at least 2 weeks of oral iron. They found that both regimens were effective, but that the group receiving rHuEPO showed higher reticulocyte counts from day 4, higher hematocrit increases from day 11 and a shorter median duration of therapy to achieve the target hemoglobin value of 11 g per dL (18 days versus 25 days) with more women reaching the target by the end of 4 weeks. The implication is that rHuEPO may not be necessary for all anemic pregnant women, but when time is of the essence, such as in a patient diagnosed late in pregnancy or when preterm delivery may be necessary, the preparation may have significant value. Similar findings have been reported in studies of women treated for postpartum anemia. (30,31).

In short, anemia in pregnancy is extremely common. It should be treated aggressively to reduce the potential risk of transfusion and possibly other risks to the fetus. (Figure 42.1) If time allows and the patient can tolerate it, oral iron is quite effective. If a woman cannot take the oral preparations or if they have been ineffective she should be given intravenous iron. If time is a factor or if severe hemorrhage is anticipated, to rapidly achieve the highest possible hemoglobin level in the shortest time, intravenous iron in conjunction with rHuEPO should be used. Further studies are needed to define the optimal dosing of rHuEPO and to identify the patients most likely to benefit from it.

CONTROLLING BLOOD LOSS

A detailed description of the all the various traditional obstetrical techniques to treat postpartum hemorrhage can be found in standard obstetrical texts (9,10). This section will focus on an overall approach to the problem and discuss in more detail some of the newer treatments and some of the controversies surrounding others.

The recognition of obstetrical hemorrhage is often difficult and therefore delayed, leading to significant blood loss prior to the implementation of hemostatic measures. Blood loss leads to hypovolemia, which in turn can quickly lead to hemodynamic instability and shock, and consumptive coagulopathy may further complicate clinical management. It is therefore vital that the clinician be alert for signs of excessive blood loss and immediately act to diagnose and treat. The obstetrician should routinely examine all postpartum patients to quickly identify any source of excessive bleeding. Early recognition of hemorrhage allows for early intervention. Evaluation should include palpation of the uterus to confirm adequate contraction and examination of the cervix and vaginal walls to identify lacerations or other traumatic bleeding sites. Should hemorrhage occur, the obstetrical team should have a rehearsed plan for how to deal with it.

The first step in treating postpartum hemorrhage is to identify its etiology. Uterine atony, which occurs in one of every 20 deliveries, is the most common cause. However, the clinician must rule out a laceration or retained placental cotyledons in order to be confident that atony is the cause of bleeding.

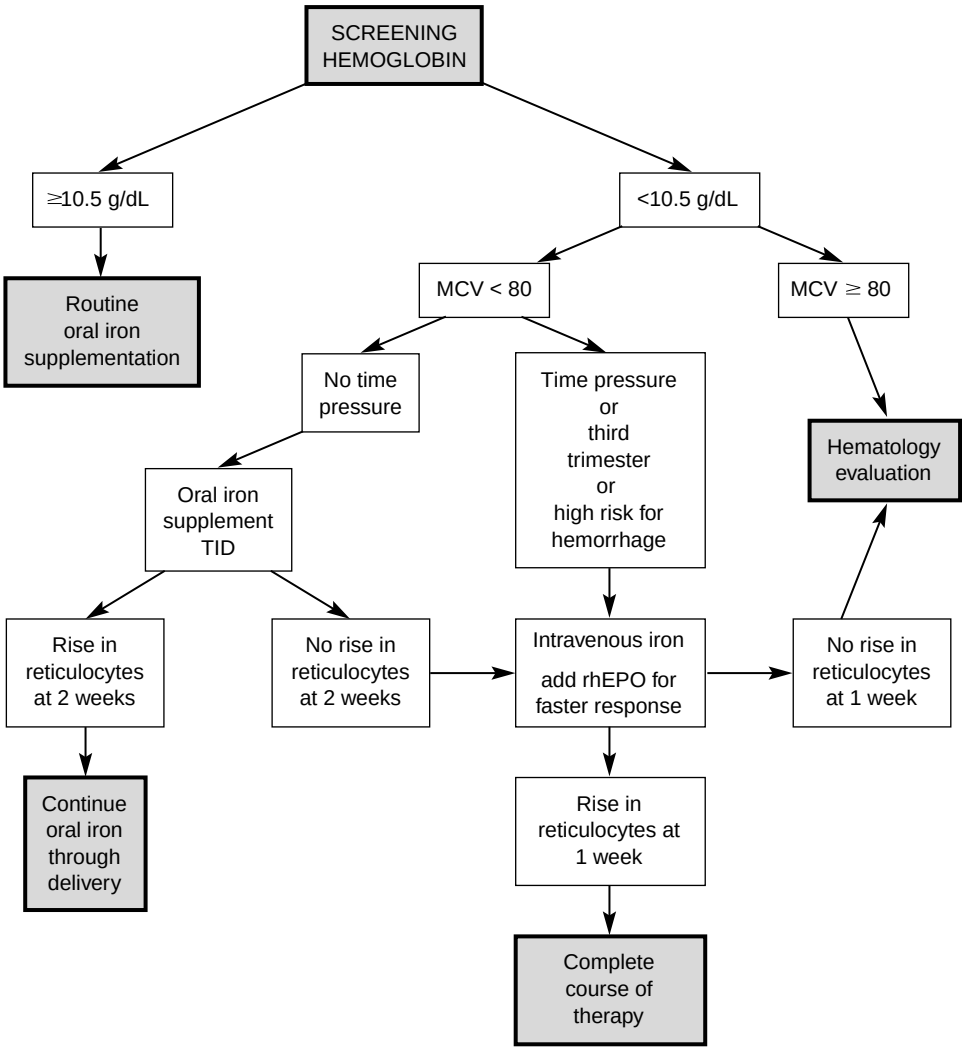

Figure 42.1 An algorithm for the treatment of anemia in pregnancy.

Medical Treatment of Uterine Atony

The first line of treatment is a combination of bimanual uterine compression and massage followed rapidly by various uterotonic medications used for their ability to cause the boggy uterine muscle to contract (32). Traditional drugs in this category include oxytocin and ergots, specifically methylergonovine (Methergine) and ergometrine. Newer agents, specifically prostaglandins, such as carboprost tromethamine (15-methyl prostaglandin F2) (Hemabate), prostaglandin E2 (Prostin E2), and misoprostol (Cytotec) a synthetic prostaglandin E1 analogue have proven extremely effective in treating and preventing atonic hemorrhage. Usually oxytocin is the first drug used, but often in insufficient doses. Munn et al. (33) found a dose of 2,667 mU per min (67 ml per min of a 1,000 ml salt solution containing 40 Units of oxytocin) significantly reduced the need for additional agents compared to a dose of 333 mU per min (19% versus 39%, $P < 0.001$).

Among the prostaglandins, carboprost tromethamine, 250 mcg intramuscularly has been shown to be effective in treating about 90% of uterine atony patients (34) when used intramuscularly, injected either into skeletal muscle or directly into the myometrium. This dose can be repeated every 15 minutes to a maximum of 2 gm, but if the first few doses are not effective, additional measures should be taken. This drug should not be used in asthmatics because of its bronchoconstrictive effect.

Misoprostol has recently received interest as a drug to prevent (35–38), and in a small uncontrolled study, (39) to treat atonic postpartum hemorrhage. It is well absorbed rectally, and when administered in a 1,000 mcg dose to 14 bleeding patients unresponsive to oxytocin and ergotrine, was effective within 3 minutes of administration. It also has the advantage, unlike other prostaglandins or ergots, of being safe in patients with asthma, hypertension, and pre-eclampsia because it is a prostaglandin E1 analogue and therefore has no bronchoconstrictive or

vasoconstrictive effects. If its efficacy is borne out in future studies, it may become the drug of choice because of its ease of administration, lack of need for refrigeration, and its extremely low cost. Roman and Rebarber (40) recommend inserting five 200 mg tablets in the bleeding parturient's rectum as soon as uterine atony is noted to be unresponsive to the traditional oxytocin and ergot. The author suggests not waiting that long, but rather using misoprostol or 15-methyl prostaglandin F2 immediately after high dose oxytocin and uterine massage are deemed unsuccessful. If medical treatment of uterine atony fails, the obstetrician must move quickly to mechanical and/or surgical intervention.

Mechanical Treatment of Uterine Atony

Among the mechanical approaches is uterine packing. This method relies on gauze packing material used to compress open uterine blood vessels within the endometrial cavity in order to tamponade bleeding. Maier (41) reported his own institution's experience with nine cases of uterine packing and wrote a thorough review of the literature on this method. He concluded that although packing had gone out of favor since the 1950s, the recently renewed interest in the technique has merit, if packing is done properly. Tight and complete packing of the entire uterine cavity seems to be a quick and effective method to treat uterine bleeding, although some experts remain concerned about the possibility that continued bleeding may remain occult because of sequestration in the gauze pack, causing delay in further treatment. Should this happen, the patient may become hemodynamically unstable and develop a consumptive coagulopathy leading to further blood loss, transfusion of allogeneic red cells and clotting factors, as well increased surgical risk and morbidity.

Several reports of various balloon catheter devices used for uterine cavity tamponade have appeared over the past 10 years (42–45). Successful treatment of postpartum hemorrhage due to atony, retained placenta, and placenta accreta has been reported with foley catheter balloons, Sengstaken-Blakemore tubes, and recently a new larger, more pliable balloon, designed and patented by Packer, (46) that accommodates to the walls of the uterine cavity to compress the entire endometrium. If successful, the balloons are generally left in place for 12 to 24 hours. The advantage to these devices is that they do not absorb blood, they have lumens that allow drainage and detection of continued bleeding and they all allow the use of ultrasound to assess accumulation of blood within the uterine cavity. Balloon tamponade may be preferable to gauze packing by allowing earlier diagnosis of failures, leading to more rapid further intervention when necessary.

If medical and mechanical techniques are unsuccessful, the obstetrician must move expeditiously to more invasive treatment. During the earlier therapeutic efforts, an operating room should be prepared for laparotomy and possible postpartum hysterectomy should that become necessary.

Surgical Treatment of Uterine Hemorrhage

Although hysterectomy is ultimately the treatment for unresponsive postpartum uterine hemorrhage, several successful uterus-preserving procedures are well known and widely used. The art in these cases is deciding when conservative therapy is too dangerous despite the physician's desire to preserve the patient's future childbearing ability. Going directly to hysterectomy may deprive the patient of a procedure that might preserve her fertility, but decrease the risks associated with her present condition. Conservative procedures have potential to preserve the uterus, but should they fail, the delay engendered increases the risk of transfusion, coagulopathy, and other surgical morbidity and mortality. It is helpful in making these decisions if the clinician knows the woman's desires for future pregnancies and any other situation that may apply. For instance, a patient who cannot accept blood products should be aware that the physician may be more aggressive in the use of hysterectomy in order to avoid life-threatening blood loss.

Uterine Compression Sutures

In 1997, B-Lynch et al. (47) described the successful use of an innovative uterine compression suture in five cases of severe postpartum hemorrhage. Several others have reported their series of compression suture use, each with a great deal of success (48–51). Although only a small group of patients have been reported undergoing this procedure, anecdotally, many other clinicians are using the technique or one of its modifications. The basic concept of all the compression suture techniques is to occlude open vascular sinuses in the uterine cavity by bringing one or a series of sutures from the lower segment of the uterus through-and-through the front and back walls of the uterus and over the top of the fundus. The suture is then tied to squeeze the uterus from top to bottom to occlude the open vessels (Fig. 42.2).

Roman and Rebarber (40) reported success in seven of eight patients. Their criteria for using the procedure is to manually compress the uterus either following vaginal delivery or directly at the time of postcesarean hemorrhage. If there is a decrease in blood flow, the suture is placed to provide continuous compression. Absorbable suture material should be used, to decrease the long term risk of bowel entrapment as the uterus involutes back to its nonpregnant size and an open loop of suture is created.

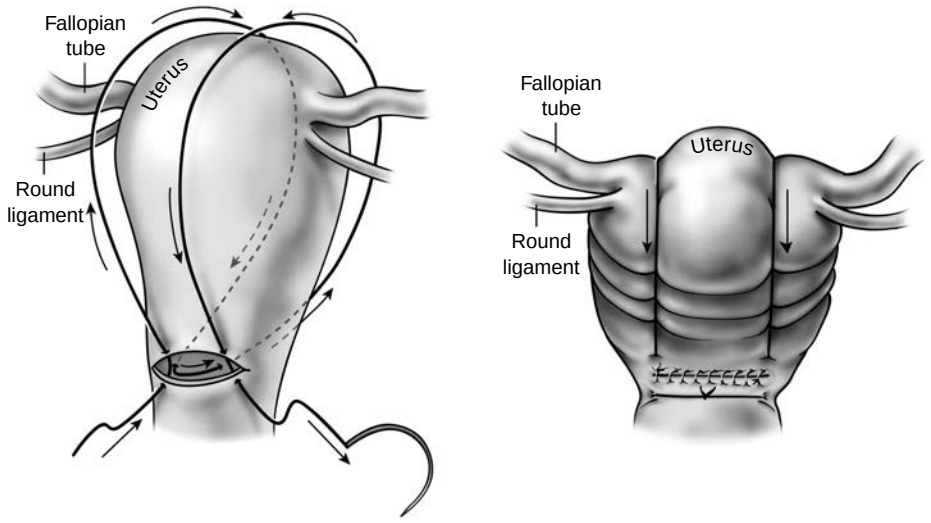

Figure 42.2 Schematic representation of the placement of the B-Lynch suture for surgical control of uterine hemorrhage.

Several studies report a few patients followed after these procedures. Thus far there have been several subsequent successful pregnancies, normal MRI, and other imaging studies, with no evidence of tubal obstruction or other complications.

Vascular Ligation

Because the gravid uterus is so vascular, receiving its blood supply from collateral circulation including arterial sources other than the uterine vessels, it is relatively resistant to complete devascularization. As a result, occlusion of the uterine arteries can successfully decrease uterine bleeding without compromising the integrity of the organ or its ability to carry a future pregnancy. Several approaches to the technique of uterine artery ligation have been described (52–55). The O'Leary technique is probably the most popular currently. The object of the procedure is to rapidly ligate the ascending branch of the uterine artery bilaterally without injuring the vessel. An absorbable suture is used so that the artery may reopen once the suture disappears. The author has come to favor the technique of placing an atraumatic vascular clamp or a rubber-shod clamp on the vessel right across the broad ligament. If bleeding decreases then the suture is placed. This has the advantage of speed, confirming the efficacy of the procedure, and reducing blood loss while the sutures are placed.

Another technique that has been widely used but is not as much in favor today is internal iliac (hypogastric) artery ligation. This technique was well studied by Burchell (56) who reported in 1964 on 13 women who underwent the procedure. He found that bilateral hypogastric ligation produced an 85% decrease in arterial pulse pressure. Theoretically it is this decrease in pulse pressure that allows decreased blood flow long enough to allow clot to form and bleeding to cease. There are several problems with the technique, however. It is technically more difficult that uterine artery ligation, it requires more training and experience operating in the retroperitoneal space, it takes significantly longer than other techniques, and it is effective less than half the time (57). In addition, because it obstructs the internal iliac artery, it prevents subsequent vascular access for selective uterine and other pelvic arterial embolization. For these reasons, the routine use of hypogastric artery ligation is not advocated.

Selective Arterial Embolization

Selective arterial occlusion for hemorrhage began as an offshoot of angiography as a treatment for gastrointestinal hemorrhage. In 1979 Heaston et al. (58) issued the first reported use of the technique in obstetrics with its use after unsuccessful hypogastric artery ligation. Since then there have been numerous reports of the technique's utility in all kinds of bleeding. It has been used in obstetrics and gynecology in the management of ectopic pregnancy, cervical pregnancy, uterine fibroids, gynecologic malignancy, postabortion bleeding, and obstetrical hemorrhage. Of particular interest for us is the use of the procedure in obstetrical hemorrhage. Depending on the situation in which it is used, it can be up to 97% effective in this latter group of patients (59). Yet selective embolization remains highly underutilized and has yet to achieve its full potential in obstetrics. The most appropriate strategy for incorporating this important technique into the obstetrician's armamentarium has yet to be defined. Every hospital with an angiography suite should develop protocols for the treatment of obstetrical hemorrhage. Every obstetrician should be educated as to the use of this procedure and its indications in these patients.

Selective arterial embolization, specifically of the uterine artery, can be used in three ways: as an alternative to primary surgical treatment for obstetrical hemorrhage, when surgical treatment has failed to correct postpartum hemorrhage, or prophylactically when serious bleeding is anticipated (for example sonographically diagnosed placenta previa or accreta).

Embolization as an Alternative to Surgery

Bilateral uterine artery ligation with or without sequential ligation of vaginal arterial branches and ovarian arteries (52–55,60) has been proven effective in stopping postpartum hemorrhage. Percutaneous uterine artery embolization is a relatively low-risk nonsurgical technique for achieving the same goal without the complications of a major surgical procedure in an already unstable patient. Furthermore, the angiographic procedure allows for easy identification of the site of bleeding, obliteration of collateral vessels leading to the same bleeding point, and confirmation of success by repeating the dye study at the end of the procedure. Its success rate of over 95% means few patients will require subsequent surgery. The disadvantage is that the procedure usually requires transfer of the patient out of the obstetrical suite for 2 or more hours at a time when she is bleeding actively. The rate of bleeding must be slow enough and the patient stable enough to allow this to happen. Of note is the fact that embolization has become a standard treatment in trauma programs, where many of the issues are similar.

Embolization as Adjunct to Failed Surgery

The first report of the use of embolization in obstetrical hemorrhage (58) was for persistent bleeding after hypogastric artery ligation. Fortunately the bleeding vessel was a branch of the pudendal artery and therefore accessible despite prior surgical obstruction of the hypogastric artery. Although embolization can be highly effective even after surgical ligation, the prior surgical procedure can make embolization difficult or even impossible. Success rates for postoperative embolization may be significantly lower than those for embolization used as primary treatment. The procedure can be used for pelvic bleeding after hysterectomy, and even in cases of coagulopathy, though failure rates may be higher.

Prophylactic Embolization

Several reports (61–63) have described the use of prophylactic placement of arterial catheters for potential embolization in high risk obstetrical cases, such as prenatally diagnosed placenta previa, placenta accreta, abdominal pregnancy, or cervical pregnancy. Arterial catheters are inserted prior to surgery either through the femoral or axillary artery and advanced to a point near the uterine artery. As soon as the baby is delivered, on the operating table under fluoroscopic guidance and prior to any further surgical intervention, embolization is performed to reduce bleeding and allow for obstetrical options to be exercised. The technique can be used instead of further surgery or to reduce blood loss prior to undertaking surgery in these situations. For instance, once embolization has been performed in a case of placenta accreta, the physician may plan to remove the adherent placenta or simply perform a hysterectomy with the placenta in situ. Either way blood loss should theoretically be reduced. The lack of controlled studies makes absolute statements about the benefits of prophylaxis impossible, but early positive clinical experiences warrant further scientific investigation of the technique.

It remains a matter of judgment, experience, logistics, and ultimately confidence in the embolization technique that will determine how the obstetrician uses it. A successful program requires close coordination between obstetricians and radiologists to design practical protocols and to educate each other about their specific needs and concerns. As this develops, it is our experience that the obstetrician begins to think of arterial embolization as the treatment of choice whenever possible, and its utilization rises rapidly.

In summary, many techniques are available to treat hemorrhage at the time of vaginal or cesarean delivery. Some are well supported scientifically. Others are more controversial. Some are new and need to be learned by obstetrical caregivers. Others like uterine artery embolization require teamwork, coordination, and education. But all have their place in caring for the bleeding patient. The most important point is that the obstetrician must know what is available and a strategy for how to stop bleeding when it occurs.

CONSERVATION OF AUTOLOGOUS BLOOD

Although most physicians would agree with the notion that unnecessary blood transfusion should be avoided, there is lack of universal agreement as to exact indications for transfusion (transfusion trigger) and insufficient knowledge of transfusion guidelines and alternatives to allogeneic transfusion. This is particularly true in obstetrics where physiologic changes of pregnancy and concerns about effects on the health of the fetus further complicate matters.

In 1988 the National Institutes of Health reported the conclusions of a consensus development conference on blood transfusion (64). They stated that the decision to transfuse should not be based on hemoglobin level alone,

but rather on the clinical status of the patient. The earlier concept that hemoglobin level should be maintained above 10 g per dL has been abandoned. More recent evidence shows that euvolemic patients can tolerate much lower levels of hemoglobin than once thought. The American Society of Anesthesiologists recently approved a recommendation that for a healthy patient red cell transfusion is usually unnecessary if hemoglobin concentration is above 6 g per dL (65). Other data suggest that oxygen delivery is not impaired in healthy normovolemic patients with hemoglobin levels of 5 g per dL (66). In other words, healthy people with normal blood volumes can tolerate anemia to a far greater extent than we previously believed.

Two recent studies, (67,68) looking at the appropriateness of transfusion in obstetric populations, demonstrate an overuse of allogeneic transfusion by physicians caring for pregnant women. In both studies physicians were found to be transfusing in excess of what guidelines recommend and in larger quantities than required per patient. Although physicians in general no longer give blood simply for hemoglobin levels below 10 g per dL, it is clear that more physician education is needed in order to manage the limited blood supply and reduce patient risk.

There is data available on three alternative methods used to reduce allogeneic red cell transfusion in obstetrical patients: preoperative (or predelivery) autologous donation (PAD), acute normovolemic hemodilution (ANH), and intraoperative blood salvage (IBS).

Preoperative (Predelivery) Autologous Donation

Preoperative autologous donation (PAD), a technique in which the patient donates blood to be held for his or her own future use in advance of a planned surgical procedure, gained popularity in nonpregnant patients in the 1980s when HIV was found transmitted through blood transfusion. Because of the potential advantages of PAD for pregnant women, interest grew in its use in this population. Because of safety and efficacy concerns, several studies were conducted in pregnant women (69,70). McVay et al. (69) reported on 268 third trimester donors who gave 341 units. Seven of the 341 (2.1%) donations were associated with minor reactions such as vasovagal responses. There were no fetal reactions to donation. Only one of the 268 patients required allogeneic blood. Twenty-four patients were transfused with their own blood, but 18 received only one unit, calling into question whether they truly required transfusion. Those patients who donated within 7 days of delivery were more likely to be transfused, raising the issue of adequate time to reconstitute the predonation hemoglobin level. Finally, 311 of the 341 units were not transfused and ultimately wasted.

The authors conclude that autologous transfusion is safe for mother and fetus, that it may encourage unnecessary transfusions, that donation too close to delivery may increase the need for transfusion, and that there is a high rate of blood wastage.

There may be a role for the use of rHuEPO as an adjunct to PAD to reduce the incidence of postdonation anemia and allow for multiple donations. This technique is widely used in orthopedic surgery and other specialties (71). Further study is required before recommendations can be made for the most appropriate use of PAD in pregnancy. Furthermore, PAD is expensive and still carries the risk of mislabeling and administration of the wrong unit of blood. With the availability of other methods of providing autologous blood, PAD should be reserved for specific high-risk patients.

Acute Normovolemic Hemodilution

This technique has been used for many years in other specialties, but not widely in the obstetrical population. The object of the ANH is to remove whole blood from the patient at the time of surgery or delivery and replace it with adequate fluid to maintain normal intravascular volume. The red cells removed are then held aside for later reinfusion once blood loss has ceased. By diluting the patient's blood, the mass of red cells lost in the blood shed during surgery or delivery is decreased, and the harvested cells previously removed can be preserved. Healthy patients can tolerate hemodilution down to a hemoglobin level of 6 to 7 g per dL or lower. The technique is safe because it avoids the risk of administrative error, since the patient and her blood are never apart. It is also a much less expensive method of obtaining autologous blood because typing, testing, storage, and transport are unnecessary.

In pregnant women, however, there are some special concerns. Is there a risk of cardiac failure due to the preexistent physiologic anemia and high cardiac output of pregnancy? Could this lead to decreased uterine perfusion and fetal hypoxia? Is the efficacy of the procedure limited by the physiologic hemodilution already in effect?

Grange et al. (72) performed hemodilution on 38 women undergoing cesarean section. Of these, 33 women had placenta previa. They removed 750 to 1,000 ml of blood to a mean preoperative hematocrit of 25%. In addition 24 of the 38 had already predonated autologous blood. Prior to reinfusion, their mean hematocrit was 22%, which was well tolerated.

There were no complications of the hemodilution procedure. The rate of transient hypotension related to this procedure was the same as that expected from epidural or spinal anesthesia alone. Only one patient required allogeneic blood. All neonates had normal Apgar scores and umbilical cord blood gases.

Although this study lacks a control group that would allow conclusions about efficacy in preventing transfusion, it does appear that ANH is safe to perform in pregnant women undergoing cesarean delivery. Further investigation is required to determine the maximum safe volume to remove, the potential role of rHuEPO given preoperatively, and the potential for use of intraoperative blood salvage in conjunction with ANH.

Intraoperative Blood Salvage

Intraoperative blood salvage (IBS) has been reported since the early 19th century. In 1818, James Blundell reported using the technique in a series of postpartum hemorrhage patients, collecting blood from the vagina. In 1874, W. Highmore recommended its use for postpartum hemorrhage. In 1980, B.S. Merrill reported on 38 cases of ruptured ectopic pregnancy treated with IBS. Despite this early experience, and despite the widespread use of the technique in other surgical situations, IBS has not yet been embraced as a routine procedure in obstetric hemorrhage. The major reason for this is concern about the possible risk of amniotic fluid embolism. Because the pathophysiology of amniotic fluid embolism is unknown, some experts prefer terms like *anaphylactoid syndrome of pregnancy* or *sudden obstetric collapse syndrome*. There is enough concern, however, that the etiologic agent is contained in amniotic fluid, that there has been some reticence to recommend the technique for obstetrical bleeding (73).

Several investigators have looked at the amniotic fluid contaminants of blood collected with cell saver technology (74,75). When combined with new generation leukocyte depletion filters, cell saver devices remove tissue factor, fetal squamous cells, lamellar bodies, alphafetoprotein, and other debris (76). Fetal red blood cells, however, remain in higher concentrations than in maternal blood. Rebarber et al. (77) reported the results of a multicenter retrospective study of 139 IBS obstetrical patients compared to 87 matched controls. They found no demonstrable increase in acute respiratory distress syndrome, amniotic fluid embolism, disseminated intravascular coagulation, need for ventilatory support, infectious morbidity, or length of postpartum hospitalization, though their numbers are too small to reach statistical significance.

To date, several hundred cases of IBS in obstetric hemorrhage have been reported. There has been a single case report of mortality following the procedure possibly related to amniotic fluid embolism. The definitive cause of death in this case is by no means certain. This patient had a preterm cesarean delivery for HELLP syndrome, a blood loss of only 600 mL, and was autotransfused only 200 mL without a leukocyte depletion filter. In 390 reported obstetric IBS cases in which salvaged blood was washed but not filtered before retransfusion, no other such cases were identified. According to Waters (76), the nonuse of filters is common practice among anesthesiologists and is probably underreported. This further supports the relative safety of IBS in obstetrics. Because amniotic fluid embolism is so exceedingly rare, an adequate controlled trial will probably never be done and the absolute safety of IBS never proven.

As to the efficacy of cell salvage in obstetrical hemorrhage, there is supporting data. Rainaldi et al. (78), in a randomized controlled trial, compared 34 women who underwent blood salvage with 34 who did not. Fewer women in the IBS group received allogeneic blood than the controls (1/34 versus 8/34).

A final mention must be given to the transvaginal use of IBS. Despite Blundell's 1818 report of success with the technique, concern about the potential risk of bacterial contamination from vaginal flora has limited its application. Although safety data are not currently available, the procedure should be considered in cases of severe vaginal hemorrhage in which allogeneic blood is not immediately available or in patients who cannot be given allogeneic blood. Prophylactic broad spectrum antibiotics may be used in these cases.

To summarize, there appears to be a role for intraoperative blood salvage and retransfusion in obstetrical hemorrhage. Although there is theoretical concern about the risk of amniotic fluid embolism, thus far there is no evidence that this exceedingly rare occurrence is increased by the IBS technique. As a precaution, prior to use of the cell saver, as much amniotic fluid as possible should be suctioned from the field using a separate suction device. Then blood salvage may begin. Leukocyte depletion filters should be used when possible, though in cases where rapid reinfusion is required, this may not be feasible. When Rh incompatibility between mother and baby is present, a Kleihauer-Betke test should be done to calculate appropriate anti-D immune globulin (Rhogam) dose.

Although the three methods discussed for obtaining autologous blood appear to be safe for pregnant women, and the blood obtained is almost certainly safer than homologous blood, reinfusion still does carry some risk and should not be done unnecessarily. Bacterial contamination, fluid overload, amniotic fluid contamination, and with PAD, misadministration can occur. Therefore, particularly with PAD and IBS, standard criteria for transfusion should be applied despite the autologous source.

CONCLUSION

This chapter has endeavored to outline an approach to treating obstetrical hemorrhage that emphasizes blood

management as one of its goals. The hallmarks of this approach include:

1. Optimizing maternal reserves by correcting abnormalities including anemia.
2. Carrying out a planned strategy for treating hemorrhage when it occurs and using appropriate pharmacologic agents and procedures with proven efficacy.
3. Avoiding allogeneic transfusion whenever possible through the use of autologous sources.

Anticipation, planning, and decisive intervention based on a logical approach to maternal hemorrhage can improve outcome with reduced blood utilization. Although much good scientific information is available on management of obstetrical hemorrhage and appropriate use of homologous blood, more research and much more physician education is needed. With an objective, thoughtful approach to blood management and conservation, maternal and neonatal outcomes will improve and the goals for treating obstetrical hemorrhage can be achieved.

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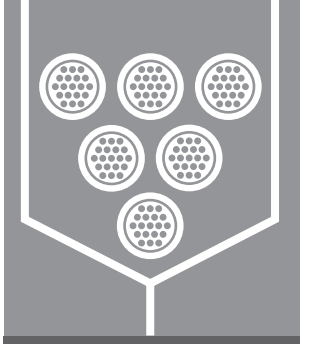

Hemorrhage in Pediatric Patients

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Thomas V. Whalen

A pediatric surgeon may see patients from in utero up to age 21 years. The average 21-year-old patient certainly will have physiology and the consequent demands and treatment that are much akin to an adult and therefore can be handled in a manner that is well described in the other chapters of this text. However, it is perhaps prudent to focus upon the early stages of life and emphasize some characteristics of basic anatomy and physiology of the pediatric patient, as it will have significant bearing upon the issues of blood volume, potential blood transfusion, and use of blood products.

Distinctions among newborns basically fit into three groups: the preterm infant, premature infant, and the infant who is small for gestational age. The definition of prematurity is admittedly somewhat arbitrarily drawn at 37 weeks gestational age. Some would also add a weight requirement with the term infant being greater than 2,500 g. While the word arbitrary has been selected, there are indeed significant issues as regards the fluid composition and the physiologic performance of the premature infant to make that specific gestational age convenient for our discussion. The small for gestational age infant is a special case.

There are various techniques that can be utilized to estimate gestational age. Many resources can be brought to bear to determine what the appropriate size for gestational age should be in regards to weight, body length, and head circumference. The underpinning fact that defines the small for gestational age (SGA) infant is that there has been some degree of malnutrition while the fetus has been developing in utero. This leads to a significant decrement in total body fat levels. Most SGA infants have less than 1% of their total body mass as adipose tissue. They therefore have less reserve and can develop dangerous levels of hypoglycemia early on. This also affects their total intravascular fluid volume. Compared to a term infant, the SGA infant has much higher red blood cell volumes and total blood volumes.

There have been enormous developments over the last four decades in the treatment of the premature infant. One central fact remains critical in our discussions in this chapter as regards the premature infant. Whereas the average adult can be estimated to have a blood volume that approximates 70 mL per kilogram, the premature neonate has a blood volume that ranges from 85 to 100 mL per kilogram. Term neonates have a blood volume of approximately 85 mL per kilogram. A significant factor that impacts the early life of the infant is whether placental transfusion has occurred. Approximately 100 mL of blood may be found in the placenta at birth. The timing of cord clamping will have an effect on the amount of blood delivery from the placenta to the infant, with later clamping leading to higher relative blood volumes.

Cell for cell, there is a noted alteration in handling of oxygen by virtue of the presence of fetal hemoglobin at birth. The P-50 value of fetal hemoglobin is 6 to 8 mm of mercury lower than that of adult hemoglobin. While in utero the presence of this fetal hemoglobin has allowed for significantly increased efficiency in oxygen delivery from the placenta to the fetal tissues. It takes fully one half year before adult hemoglobin becomes predominant enough to shift the hemoglobin curve to the right to approximate the curve of an adult.

PREMATURE NEONATES IN THE NICU

The most common *emergent* surgical intervention for patients in the neonatal intensive care unit is exploratory

laparotomy for necrotizing enterocolitis with perforation (1,2). Over the past decade there has been a move to simply place a Penrose drain into the peritoneal cavity of small premature infants who perforate their intestinal tracts (3,4). In either case, the surgeon must be concerned with the relative blood volume of the neonate who becomes the surgical patient. The most common *elective* surgical procedure performed upon premature birth neonates is now inguinal hernia repair. Previously it was placement of silicone catheters but the advent of percutaneously inserted central catheters has made this procedure rather uncommon.

The overwhelming majority of neonates who spend any appreciable amount of time on the neonatal intensive care unit will have red blood cell transfusion and potentially transfusion of other blood components (5). The single biggest factor in the requirement for transfusion over days to weeks lies in the fact that phlebotomy is performed for various blood tests leading to physiologically significant anemia. In neonates identified antenataly to have defects that will require operative intervention with projected significant blood loss, one can consider banking autologous cord blood to be administered at the time of need during surgical intervention (6).

Among normal neonates, especially those who are breast-fed, the surgeon must always be aware that there may be vitamin K dependent bleeding (7). Any exclusively breast-fed infant should most assuredly receive an injection of vitamin K well in advance of any elective operative procedure and as near to any urgent or emergent operative procedure as is practical.

TRAUMA

Hypotension is generally well regarded as a significant indicator of volume loss in the traumatized patient. It is perhaps generally considered more reliable in the child than in the adult as there are few if any confounding factors. The physiology of the child however may as always surprise. Among children who are traumatized, the greatest reason for fatality is significant head injury. Throughout the pediatric age range, up to one third of traumatized children presenting with hypotension may not have significant volume loss but may indeed be hypotensive secondary to closed head injury (8).

Pediatric surgery spawned the development of nonoperative management of solid organ injury. Prior to the mid-1970s any injury to the spleen or perhaps even suspicion of injury to the spleen led to exploratory laparotomy. Evidence of bleeding from the spleen of any degree was sufficient indication to remove that organ. The pioneering effort to avoid splenic removal was founded at the Toronto Hospital for Sick Children (9). The basis for this therapeutic revolution was the recognition of and the desire to avoid the entity of overwhelming, postsplenectomy infection. Nonoperative treatment did not gain immediate acceptance even within the pediatric surgical community. The development of this approach in the 1970s was followed shortly by the onset and recognition of contamination of the blood supply by the human immunodeficiency virus. At the time of the original report of nonoperative management, it was accepted at the originating institution and gained slow but steady acceptance as a standard of care in pediatric trauma. The nonoperative treatment protocol recommended that a child with an injured spleen could undergo transfusion of 40 mL per kilogram of blood before operative intervention was entertained. This volume represented fully 50% of the child's blood volume.

Just beyond the end of the first decade of this therapeutic strategy, the group in Toronto updated their results, providing lessons learned as well as implications for strategic management of the child with the injured spleen (10). These issues included: (a) most children with splenic injury could be successfully treated without operation (87%), (b) those who were hemodynamically stable did not require a stay in the pediatric intensive care unit, (c) the total hospital stay for uncomplicated splenic injury could be limited to 7 days, and (d) laparotomy could be safely reserved for patients with immediate massive hemorrhage or with transfusion requirements of greater than 40 mL per kg.

Nonoperative management of splenic trauma is now widely accepted in both children and adults and has even been reported in a neonate with splenic injury secondary to birth trauma (11). Currently, the standard of allowing up to 50% of blood volume to be transfused in nonoperative management of solid organ injury, especially as regards the spleen, is no longer widely accepted because of increasing awareness of the risks of transfusion, particularly among the public. Hemoperitoneum in the child needs to be quantified rather than just established as being present or not. This is why peritoneal lavage is rarely if ever indicated in the child. Currently, many centers employ ultrasound not simply to establish whether or not blood would be present in the child's abdomen but also to quantify the amount of blood and therefore to make a decision as to whether or not operative intervention must be entertained (12).

In the early years of treating patients nonoperatively with splenic injury, it was uncertain what level of activity should be allowed for the child and adolescent following such a therapeutic strategy. Conservatism usually prevailed such that there were prolonged intervals prescribed without any foundation as to how long activity should be restricted. Over time, these intervals shortened to where it

is now generally accepted that as little as 2 months of restrained physical activity is all that is necessary. In addition, imaging of the spleen as a follow-up assessment is no longer indicated (13).

Nonoperative management of solid organ injury long ago extended beyond the spleen to the liver as well. Clearly, operative control of the bleeding liver is a daunting task at best because profound hemorrhage may ensue. Initial anecdotal observations at the time of laparotomy prompted by positive peritoneal lavage of lacerations of the liver that had long stopped bleeding suggested that nonoperative management of these injuries was acceptable therapy. Large series have shown that about three quarters of children with bleeding from hepatic injury may be observed successfully without operative intervention (14). Even in the case of significant hemorrhage from the liver with blunt injury one may consider nonoperative management while employing radiographically guided transcatheter embolization techniques (15).

There remain sporadic case reports of nonoperative management of liver injury with untoward outcomes or at least significant morbidity (16) that may have been averted by earlier operative intervention (17). Clearly, the now well demonstrated success of nonoperative management in splenic trauma in both children and adults is not uniformly seen in hepatic trauma. Recent utilization of evidence-based guidelines for nonoperative management of solid organ injuries articulated and circulated by national societies have demonstrated that this approach can decrease overall length of stay, stay on the pediatric critical care unit, and overall consumption of health care resources without any change in outcome (18).

Many pediatric centers treat the injured kidney in the same fashion as the spleen or other solid organs with significant parenchymal injury. Such a philosophy of treatment can extend throughout the spectrum of renal injury from grade I through V (19). As many as 40% of these injuries may be treated nonoperatively with preservation of renal mass and without subsequent hypertension, even at the high end of the injury scale. Transfusion amounts stratified by grade are quite reasonable and in line with nonoperative management of other solid organs that are injured. Yet, ironically, with hemorrhage there may be significant renal damage despite resuscitation including red cell transfusion, (20) suggesting that we need further investigation to determine the best strategy for high grade renal injury with bleeding.

Pelvic fractures in both children and adults can produce exsanguinating injury. Traditionally it has been held that pelvic fractures may be milder in the child than in the adult (21). At least one large series, however, disputes this assumption (22). In this comparison of patients with pelvic fractures separated into age levels of younger or older than 16 years, there was no difference between the groups in the number of associated intra-abdominal injuries and relative rates of transfusion. It is however noteworthy that the only fatalities were seen in the adult group.

ETHICS OF TRANSFUSION IN PEDIATRICS

The ethics of transfusion in the adult patient refusing such therapy based upon religious principle has long been settled. This is of course chiefly seen in the setting of the patient who holds to tenets of the Jehovah's Witness faith. While there may certainly be some physicians and other health care providers who have misgivings about honoring such beliefs, it is clear that ethically and legally any provider encountering such patients judged to be competent (as almost all certainly will be) must honor their stated preference.

In most clinical environments in the United States, it remains a standard practice to *not* honor a parent's expressed desire to not have their child transfused when it is deemed critically important for the survival of the child to undergo such therapy (23). In such circumstances if the matter is not absolutely emergent it is common practice to seek a court order for transfusion, and such court orders are generally given. In emergent circumstances, practitioners will generally give blood to a child as an incompetent minor over the desire of the parents to not have their child transfused for religious reasons.

After extensive review, I find no successful tort action having been brought against a practitioner who has transfused a child against parental desire. On the other hand, I am not personally aware of any physician who has agreed to parental desire and belief not to transfuse a child who has died subsequently due to the attendant anemia. There may certainly be such instances that understandably have not been published.

On the ethical forefront, the most troubling issues undoubtedly arise in the instance of adolescents undergoing operative procedures, particularly elective operations (24). No one is foolish enough to think that a patient who is 17 years old on the day before their 18th birthday is entirely incapable of thinking for themselves in making decisions based upon their own inherent religious beliefs and yet magically after a good night's sleep awakening on their 18th birthday they have gained such capacity. The legal age of majority is simply that: a legal definition. There are many who are perhaps even long past their 18th birthdays that test anyone's definition of having achieved independent decision making. The ethical, legal, and medical

quandary arises when one treats a 17-year old or 16-year old or perhaps even in some instances 12-year old or 13-year old who clearly and unequivocally state in a mature fashion that they have made the decision based upon fervently held religious principle to avert transfusion in any circumstance. In other countries, there may be less legal paranoia about the obligation to reach the legal age of majority before one can make an independent decision (25). The final decision about the rights of this *mature minor* rests with the courts.

In an era when blood and component transfusions are used more carefully due to infectious concerns, it is prudent to look to the experiences that centers have had in attempting to avoid or at least minimize the use of blood products in specific pediatric populations. When an adolescent population with malignancies was treated by standard chemotherapy but in addition received supplementation with iron, human erythropoietin, interleukin 11, granulocyte colony-stimulating factor, and autologous or allogeneic stem cell rescue, equivalent oncologic therapeutic outcomes were achieved but with 39% fewer red cell transfusions and 37% less platelet transfusions (26).

In any center where they are or may be significant numbers of patients refusing blood products based upon religious principle, i.e., Jehovah's Witnesses, we strongly advise open communication and advance planning with both the child's family and the Hospital Liaison Committee members of the religion to gain mutual insight into the issues effecting one another's beliefs and practices and to avoid conflict as much as possible at the point of treatment.

TECHNIQUES

It always bears repeating to state the obvious but not always employed adage that avoidance of the need for transfusion begins with effective surgical technique. Fastidious prevention and expeditious control of hemorrhage surgically must always be in the forefront of the surgeon's mind. This philosophy is ever the more important for the pediatric surgeon. Keeping in mind the basic coagulation mechanisms that are largely equivalent to the adult in all but the neonatal population is also of great merit in avoiding the need for red blood cell administration or other blood components.

Despite many advances over the past two decades in various techniques to minimize or even avoid blood transfusion or transfusion of blood components, there remains a vacuum of information as to the scientific basis for indications as to transfuse or not. It is perhaps all the more confusing when dealing with the child with considerably smaller margins of error. In a review of pediatric transfusion therapy published in 1992 (27) the following was stated, "It has become clear that most surgical patients tolerate a hemoglobin level $<$10 g per dLwithout any increase in perioperative morbidity... unfortunately, assessment of the need for transfusion is difficult and remains inexact". A more recent review published in 2004 (28) revealed this continued lack of clarity, as reflected in the statement that "despite the limited clinical evidence, there are many guidelines that address transfusion practice in critically ill children...[with] suggested transfusion thresholds from major textbooks ranging from 4.0 to 16.0 g per dL for different underlying conditions". Except for pediatric cardiac patients for whom higher hemoglobin levels are advocated, there is a dearth of evidence upon which to base the decision for or against transfusion in specific settings.

The pediatric surgeon's decision to use blood has been further complicated by recent evidence from case control studies of critically ill children showing that transfusion is independently associated with an increase in days of oxygen therapy, days of mechanical ventilation, days of vasoactive agent infusions, and an increase of PICU and hospital lengths of stay—all adverse outcomes (29). In an editorial commenting upon this study, it was asserted that "clinical therapies, such as transfusion of red blood cells or administration of albumin for critically ill patients, are common but may not lead to improved results of organ function and survival. The current studies suggest that lower hemoglobin concentrations are well tolerated by many groups of patients, and that administration of red blood cells may have unintended negative consequences; however, more studies are needed to evaluate pediatric patients, particularly neonates and children with congenital heart disease" (30) One solid effort in this direction is the development of guidelines for pediatric transfusion stratified by age (31).

Recent writings on treatment of burn victims further demonstrate the need for individualized transfusion decisions, as stated by Palmieri (32): "Blood transfusion thresholds in burns vary based on burn percentage, age, and presence of cardiac disease. To date, no standard of care exists for blood transfusions in burns". Within that field of burns in children there is early evidence that transfusion requirements are decreased by early definitive burn wound excision (33).

Despite the lack of an evidence-based standard underlying the transfusion trigger point, it is necessary in surgical and anesthetic practice to have an estimated allowable blood loss for any procedure, in which either significant blood loss is anticipated or the patient has presented with an already suboptimal red blood cell mass. A generally

accepted formula that may be used to calculate allowable blood loss is (27):

$$ABL = Wt \times EBV\ X\ (H_0 - H_1) / H_{avg}$$

Where Wt is the patient's weight in kilograms, EBV is the estimated blood volume expressed as mL per kg, H_0 is the starting hematocrit, H_1 is the lowest acceptable hematocrit, and H_{avg} is the average of the initial and lowest acceptable hematocrit. The remaining *art* of medicine lies in defining for any given patient what the lowest acceptable hematocrit might be. In pediatrics, and especially in neonatal surgery, the margin of acceptable error remains small. As an example, a premature neonate weighing 1,200 grams with an initial hematocrit of 31% who is about to undergo repair of esophageal atresia and tracheoesophageal fistula might be judged unable to tolerate a hematocrit less than 25%. This baby would be allowed a blood loss of just 31 mL before transfusion would become necessary—an amount that could be easily soaked into one operative sponge.

Traditional target levels for operative platelet transfusion have been a platelet count of between 50,000 and 100,000 platelets per microliter. However, there is little solid evidence to support this *trigger*, much akin to that of red blood cells. When operative intervention is not envisioned, such as in the pediatric oncology patient, a platelet count of 20,000 has been generally accepted. Recent evidence suggests that lowering that target to 10,000 can be achieved without extra morbidity, (34) and thereby raises at least the question of studying the basis for the previously mentioned target for the preoperative child.

Hemodilution

Hemodilution has been used successfully in children and adolescents. Since its utility lies with elective operations, it is perhaps most often efficacious in orthopedic spine surgery (35). Principles utilized in this cited study included (a) autologous blood predonation, (b) controlled hypotensive anesthesia, (c) intraoperative salvage of shed blood (cell saver), (d) acute normovolemic hemodilution, and (e) transfusion decisions based upon clinical judgment rather than by a preset value of hemoglobin. Using these principles the requirement for transfusion decreased from 70% of patients to 37%. In addition, the limits of safe hemodilution (36) have been advanced to extreme levels the past decade but in children there is remarkable tolerance. Pushing such limits is aided by mathematical modeling (37).

In living donor-related hepatic transplantation in children, an increasingly favored technique due to organ shortages, dilution has been successfully utilized by replacing intraoperative blood and transudative losses with colloid solutions and a more selective use of packed red blood cells (38). Nearly half of the 48 patients did not require red call transfusion during the entire hospitalization and no negative impact upon outcome of patient or graft was seen. In othotopic liver transplantation in children, investigation has been carried out into the use of aprotinin to decrease transfusion requirements (39). While statistical significance was not achieved the trend is positive and bears further investigation.

Red Cell Reutilization

Collection and retransfusion of red blood cells has been successfully used in children and adolescents for many years (40). Cranial vault reconstruction, generally for craniosynostosis, is an example of an elective procedure with a predictable, significant blood loss that can be done with the use of a cell saver. In a series of 60 consecutive reconstructions (47% as secondary reconstructions) Fearon (41) demonstrated that with an average estimated blood loss of 356 mL, one could recover with a cell saver a mean amount of 110 mL, thereby reducing the number of patients that required allogeneic blood by approximately 70%.

Fearon (42) has also demonstrated with the same diagnosis of craniosynostosis that erythropoietin may be used successfully to decrease the need for blood transfusion in correction of this problem. In this single blinded study, only 57% of patients administered erythropoietin required transfusion while 93% of the control group were transfused.

Directed Donation

In the 1990s, parents were mortally afraid that transfusion might transmit the HIV virus to their child. While a small risk of contamination still exists for blood donated during the small window between contraction of the virus and sero-conversion, the angst of parents facing this therapeutic decision point is still high. It is therefore extremely common, despite the low risk of HIV transmission and of other blood-borne pathogens, for parents to seek directed donation despite evidence that the volunteer blood pool is at least as safe as that of directed donation. In at least one setting it has been further demonstrated that a directed donation program has a high wastage rate, is time-consuming, labor-intensive, and an expensive alternative when compared with the provision of nondirected volunteer blood (43).

CONCLUSION

Surgery in the child and adolescent brings special considerations, starting with their relatively low blood volumes and

unique physiologic response to operation. Even more than in the adult population, there is a dearth of evidence-based medicine in consideration of the need for transfusion of red blood cells and other blood components in the child. Considerable and diligent investigation remains to be done in setting evidence-based standards for treatment of hemorrhage in the child and adolescent.

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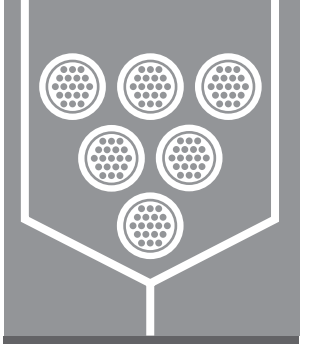

Transfusion in Oncologic Surgery

44

Patricia A. Ford *Jason Mastoris*

The oncologic patient faces unique hematologic issues while preparing for surgery. Many patients with cancer have preexisting anemia that is often multifactorial, related to the underlying malignancy, treatment, malnutrition, or occult blood loss. There is a sense of urgency associated with surgery once the cancer diagnosis is established, and this may account for the fact that preoperative priming with erythropoietin and iron or preoperative donation of autologous blood are traditionally not offered. Intraoperative cell salvage may not be considered because of the fear of transfusing malignant cells.

Although the risks of transfusion-associated infection and adverse reactions are quite familiar to doctors and patients, physicians may transfuse more readily in the cancer individual because of preconceived notions that they will not survive long enough to experience any serious complications. To the contrary, the oncologic patient who is already immunocompromised when given blood transfusions may experience an increased risk of infection and cancer recurrence. This group of patients poses an increased risk of bleeding related to underlying thrombocytopenia, coagulopathy, or chronic anticoagulation. Malignancy itself is a hypercoagulable state, increasing the risk of perioperative thrombosis.

This chapter focuses on the issues pertaining to both anemia and transfusion in the oncologic surgical patient as well as techniques for providing nonblood management in this population.

ANEMIA IN ONCOLOGY

The incidence of grade 3/4 anemia, evidenced by a hemoglobin (Hb) level less than 8 g per dL and considered severe enough to require transfusions, is as high as 50% to 60% in patients with lymphomas and certain solid tumor populations—namely lung, ovarian, and genitourinary cancers (1). The incidence and severity of treatment-related anemia for a specific malignancy are dependent upon a number of pretreatment factors (Table 44.1) (1,2). These include the history of myelosuppressive anticancer therapy, the baseline Hb level, and patient-related factors such as underlying comorbidities. The severity of anemia-associated symptoms is increased in patients who are elderly or have impaired pulmonary and/or cardiovascular function. Specifics regarding the chemotherapy regimen that are known to influence the incidence and severity of anemia include the type of agent(s), the dose intensity, and the schedule. A retrospective review by Groopman and Itri (1) found that the incidence of grade 1/2 anemia, defined as a Hb level at least 8 g per dL but not within normal limits, is approximately 75% among patients receiving docetaxel-based or vinorelbine-based chemotherapy for non-small–cell lung or breast cancer. The number of cycles received also significantly affects the risk for developing anemia. In a study conducted in the United Kingdom, the proportion of patients with anemia (Hb $<$11 g per dL) increased from 17% prior to the first cycle of chemotherapy to 35% by the sixth cycle of treatment (3).

Anemia that develops or is exacerbated as a result of oncologic surgery has the potential to delay the initiation of adjuvant chemotherapy and/or radiation. The presence of anemia can have other considerable clinical consequences for patients in terms of quality of life and clinical outcome, including an increased risk of transfusion. Cancer-related anemia produces a variety of physical and

TABLE 44.1
RISK FACTORS FOR THE DEVELOPMENT OF CANCER-RELATED ANEMIA

- History of transfusion in the past 6 months.
- History of prior myelosuppressive therapy.
- Myelosuppressive potential of current chemotherapy regimen (i.e., agent, schedule, duration).
- Baseline hemoglobin level.
- Age of patient.
- Underlying medical conditions.

psychological consequences (e.g., fatigue) that diminish patient quality of life (4). The negative effect of anemia on quality of life is underscored by the body of literature demonstrating that treatment of anemic patients with hematopoietic therapy significantly improves functional status and quality of life during chemotherapy (5–14).

Results from recent surveys indicate that a large proportion of patients with cancer-related anemia do not receive early and adequate intervention/correction. For example, in the European Cancer Anemia Survey (ECAS), only 47% of patients with hematologic malignancies and 36% with solid tumors who were anemic received antianemia therapy (15–17). In these patients, the point at which treatment was initiated was lower than is currently recommended (i.e., generally ≤10 mg per dL) (18). The mean level at which treatment was initiated was 8.8 g per dL, 8.9 g per dL, and 9.6 g per dL for patients with hematologic malignancies, multiple myeloma/lymphoma, and solid tumors, respectively. In another European survey, the overall rate of anemia in pediatric oncology centers was 81% and the rates were generally consistent across countries (19). The incidence was highest for leukemia, (97%) lymphoma, (93%) and bone cancer (78%). Treatment of cancer-related anemia consisted almost entirely of blood transfusions. Even at large institutions, less than 5% of patients received drug therapy for anemia and, when given, it consisted almost exclusively of folic acid or iron.

The decision to transfuse the oncologic patient should be based on clinical symptoms that persist after volume resuscitation (such as hypotension) and dyspnea unrelieved by oxygen, lightheadedness, syncope, chest pain, palpitations, decreased urinary output, and change in cognitive function. Multiple factors other than the Hb value can be used to determine the need for intervention (Fig. 44.1). One should attempt to identify the expected blood loss associated with a specific type of surgical procedure, allowing a target Hb to be identified. The most common cancer diagnoses in the United States are breast, lung, colorectal, and prostate carcinomas. High blood loss procedures are those typically associated with vascular, orthopedic, cardiac, genitourinary (such as radical prostatectomies), and gynecologic (hysterectomy) surgeries. Average blood loss is approximately 1,500 mL for radical hysterectomy, with 50% to 80% of patients requiring transfusion, (20) and is typically in the range of 500 to 1000 mL based on recent experiences with radical retropubic prostatectomy (21–23). Some gastrointestinal surgeries may also result in large blood losses, especially if hepatic resections are being performed. Schmidt et al. (24)

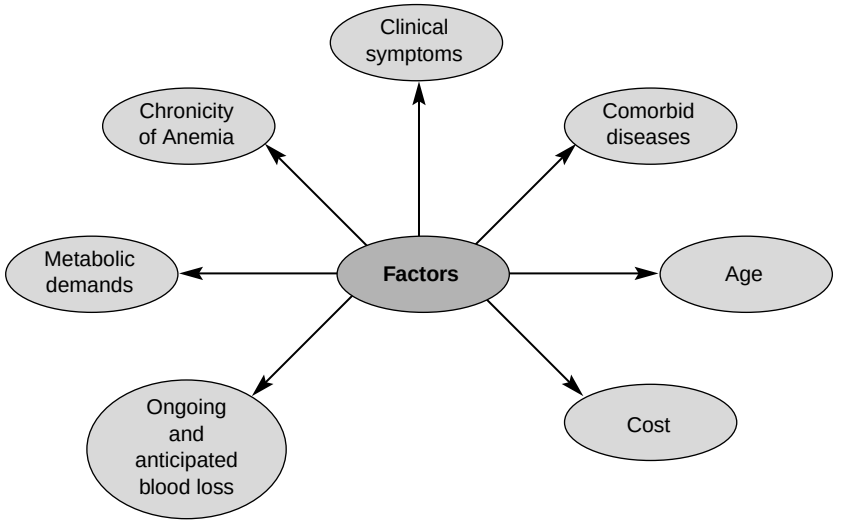

Figure 44.1 Factors influencing the decision to correct anemia.

conducted a 20-year review of 516 patients undergoing pancreatic duodenectomy, reporting a mean blood loss of 1,922 mL (median = 1,300 mL) and that patients required an average of 2.8 units of packed red blood cells (RBCs) (median = 1.5 units).

TRANSFUSIONS AND PERIOPERATIVE INFECTIONS IN ONCOLOGY PATIENTS

Although transfusions of RBCs are effective for ameliorating anemia, transfusions are associated with well-known risks, primarily related to the risk of transmission of infectious disease. Screening of the blood supply has substantially reduced the risk of transmitting HIV and hepatitis C (25). However, the potential for transmitting other infectious organisms remains. At the time of this writing, nucleic acid technology screening is not available for viral entities such as hepatitis A and B and Parvovirus B19. Transmitting parasitic contaminants, including malaria and *Trypanosoma cruzi* (the organism responsible for Chagas' disease), is also a concern that cannot be alleviated via contemporary routine blood screening.

Data from over 30 observational studies suggest that blood transfusions are also associated with up to a 10-fold increased risk of developing postoperative infections (26). For example, data from the Project IMPACT database that included 1,717 patients admitted to a medical–surgical–trauma intensive care unit found that the nosocomial infection rate for those receiving a transfusion was 15.4% compared with 2.9% for those who did not receive a transfusion ($P<0.005$) (27). The risk of nosocomial infection was dose dependent. For each unit of packed RBCs infused, the risk of developing a nosocomial infection increased by a factor of 1.5. A subgroup analysis found that there was an increase in the risk for nosocomial infection regardless of age.

IMPACT OF ANEMIA AND BLOOD TRANSFUSIONS ON CANCER RECURRENCE AND/OR SURVIVAL

Impact of Anemia

A number of studies have found that anemia is a strong predictor for adverse clinical outcomes in both medical and radiation oncology settings (28–33). Bokemeyer et al., (28) in their evaluation of patients undergoing high-dose chemotherapy for metastatic testicular cancer, documented correlations between (a) baseline Hb and time to first infusion and (b) postchemotherapy Hb and 3-year survival (87% and 68% for anemic and nonanemic patients, respectively; $P<0.03$) (28). In a meta-analysis by Caro et al., (29) which did not take into account type of treatment, the risk of death among patients with anemia was increased by 19% for those with lung cancer, by 47% for those with prostate carcinoma, by 67% for those with lymphoma, and by 75% for those with head and neck carcinoma (Fig. 44.2). Overall, there was a 65% increased risk of death for patients with anemia compared with those who did not have anemia. The data suggested that the relationship between anemia and survival was independent of disease stage/severity (i.e., anemia is an independent predictor of survival).

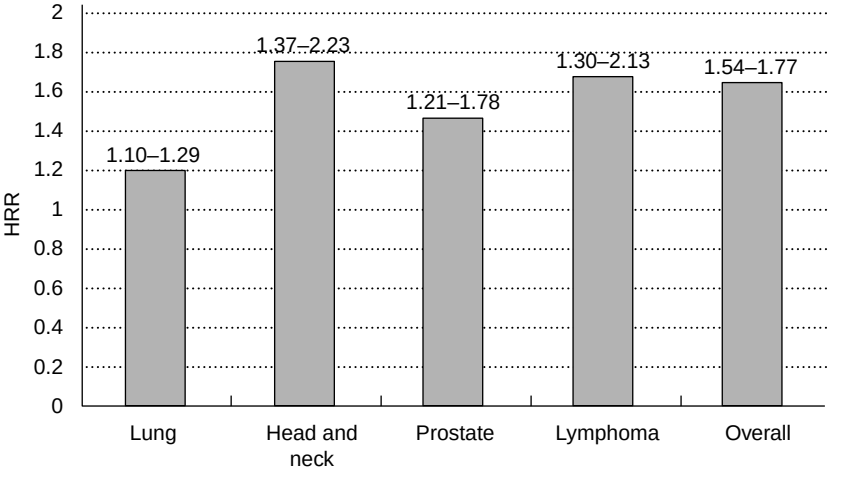

Figure 44.2 Adjusted hazard rate ratio (HRR) and 95% confidence interval for survival by tumor type. (Adapted with permission from Caro JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systematic, quantitative review. *Cancer.* 2001;91:2214–2221.)

There is a vast amount of data supporting the prognostic impact of anemia in the radiation oncology setting, a topic recently reviewed by Harrison et al. (34) In one of the most recently published studies, involving patients undergoing definitive radiotherapy for cervical cancer, there was a graded decrease in local control rates with lower pretreatment Hb levels (31). The 3-year local control rates were significantly different when assessing patients with a pretreatment Hb level exceeding 13 g per dL (85%) versus 11 to 13 g per dL (76%) versus lower than 11 g per dL (60%); corresponding 3-year survival rates were 67%, 63%, and 28%, respectively ($P = 0.003$). Hb level at baseline and mid-therapy were determined to be two of the most important prognosticators for survival. In another recent report, multivariate analysis found that a low Hb level was a significant predictive factor for both local control and survival following primary surgery and adjuvant radiotherapy for head and neck cancer (33). Relative to the subset of patients with a Hb lower than 13 g per dL, patients with a Hb 13 g per dL or higher had an a) 89% lower risk for the development of locoregional failure and b) 65% lower risk of death.

The reason why anemia is predictive of poor clinical outcome is unclear. Some investigators have suggested that anemia produces hypoxia in tumor cells, resulting in an increased resistance of the tumor cells to treatment with radiation or chemoradiation (31,32,34). Another possible mechanism is that hypoxia is a major stimulus for the development of angiogenesis, the development of new blood vessels that is associated with growing tumors (31).

Impact of Transfusion

Several studies have identified allogeneic transfusion as a potential risk factor for increased disease recurrence and a shorter duration of survival among patients with cancer (35–42). Although an adverse effect on survival has not been reported in all published series, patients who receive perioperative transfusions have been shown to have lower overall and/or disease-free survival rates in a wide variety of tumor types including colorectal, (35,42) hepatocellular, (36,38) gastrointestinal, (37,41) cervical, (40) and breast (39) cancers. For example, in an analysis of 1,710 patients who underwent curative gastrectomy for stage III/IV gastric cancer, the cumulative survival rate was significantly higher among those who did not receive perioperative transfusion (74%) compared with those who were transfused (56%, $P<0.0001$) (37). Notably, the effect on survival was related to the amount of blood transfused ($P<0.0001$). The 5-year survival was higher among those who received one to two units (61%) compared to those receiving three to four units (55%) and those receiving more than four units (38%). The effect remained after controlling for established risk factors in the multivariate regression analysis (relative risk = 1.55; 95% CI = 1.24, 1.95; $P = 0.0008$).

In a retrospective analysis of 863 patients who underwent a mastectomy for breast cancer, overall, local recurrence-free and metastases-free survival were all significantly lower in patients who received blood transfusions in the postoperative period compared with nontransfused patients (39). The multiple regression analysis showed that the effect of receiving a transfusion, specifically within 8 days of surgery, on overall and metastases-free survival was independent of established risk factors. Similar results have been reported in radiation-treated patients with cervical cancer (40). After adjusting for various prognostic factors (e.g., chemotherapy, age, histology), patients who received a transfusion during radiation or chemoradiation had a risk of death that was increased by a factor of 2.5 when compared with those who did not receive transfusions. The effect was evident both in patients with stage III disease (risk ratio = 3.2) and for those with stage IIB disease (risk ratio = 1.9).

The mechanism by which transfusions adversely affect survival has not been definitively established; however, it is speculated that it may be related to transfusion-related immunosuppression (43). The antigens infused during allogeneic transplantation produce a wide variety of adverse reactions that likely stem from the production of antibodies and specific cytotoxic T-cells, as well as the suppression of immune responses (26). Leukocytes are a known contaminant of RBC and platelet transfusions. Some data have suggested that the immunomodulatory effects associated with allogeneic leukocyte transfusion are associated with worse clinical outcome and that leukoreduction techniques can help avoid this effect. For example, in a randomized controlled trial among patients undergoing cardiac surgery, leukocyte-depleted blood was associated with a postoperative mortality rate that was lower than that of nondepleted transfusions by more than 50% (44). However, in a more recent study at this same institution, there was no significant benefit on cancer recurrence or overall 5-year survival in colorectal cancer patients receiving perioperative leukocyte-depleted transfusions (42).

A meta-analysis was recently conducted to assess whether leukoreduction is effective in reducing the risk of postoperative infections (45). This analysis pooled data from randomized trials involving patients undergoing a wide variety of surgery types. The overall risk of postoperative infection was reduced by 40% among transfused patients who received leukoreduced blood compared with those who received non-leukoreduced blood. There was also a 39% reduction in mortality for those receiving leukoreduced versus non-leukoreduced blood.

BLOOD CONSERVATION TECHNIQUES IN ONCOLOGIC SURGERY

Nonblood alternatives in the oncologic surgical patient can be separated into three phases. Options in the *preoperative* phase may include early implementation of erythropoietin and iron to avoid treatment-related anemia or correct it if present before surgery (46,47); nutritional supplementation including iron, folate, vitamin C, B complex, and vitamin K; and autologous donation of blood. In the *intraoperative* phase, patients may undergo cell salvage, acute normovolemic hemodilution (ANH), or anesthetic techniques (46,47). Finally, in the *postoperative* phase, efforts can be made to minimize iatrogenic blood loss and/or enhance hemostasis with antifibrinolytic agents. Given the complexity and cost of many of these nonblood alternatives, identifying patient variables predictive of risk of subsequent transfusion is of interest; however, little information is currently available (48–50). Some factors that appear to predict for perioperative transfusion in the oncologic surgical population are presented in Table 44.2.

Preoperative Phase

Autologous Donation

The use of preoperative autologous donation increased substantially with the advent of HIV, (51) but its popularity has since waned in conjunction with advances in blood screening. Advantages to using autologous blood transfusion include the avoidance of red-cell alloimmunization and transfusion-transmitted disease, although the risk of bacterial contamination is not ameliorated (51).There are other limitations regarding the use of preoperatively collected autologous blood, including but not limited to the risk of clerical error, the potential for a high degree of wastage of unused units, and the high costs associated with the procedure. Preoperative autologous donation may worsen the anemia already associated with malignancy and, subsequent to the donation, oncologic surgical patients may not be able to mount an adequate Hb response as rapidly as patients without cancer.

TABLE 44.2

PREDICTIVE FACTORS FOR PERIOPERATIVE TRANSFUSION IN THE ONCOLOGIC SURGICAL PATIENT

- Hemoglobin <10 g/dL related to the presence of chronic anemia.
- High blood loss procedure.
- Underlying coagulopathy.
- Perioperative coagulation or use of NSAIDs.
- Depleted iron stores
  - Malnourishment.
- Failure to identify iron deficiency
  - Ongoing occult blood loss.
  - Need for supplemental iron before starting erythropoietic therapy.
- Presence of cardiopulmonary or vascular disease.

USE OF ERYTHROPOIETIN

Recombinant human erythropoietin has been used in treating the anemia associated with HIV, renal disease, cancer, and anemia of chronic disease. Despite its FDA approval in 1996 for use in the presurgical setting, clinicians often do not think of optimizing a patient's Hb level preoperatively via erythropoietin. The use of erythropoietin and iron can facilitate preoperative autologous donation (52). One may have concerns that the oncologic patient known to have a blunted erythropoietic response, inadequate iron stores, and diminished delivery of iron through erythropoietic precursor cells may not be able to sufficiently increase their Hb in order to predonate. There are studies that have specifically looked at preoperative recombinant human erythropoietin in oncologic surgical patients and have shown an increased yield of autologous blood, (53,54) as well as the ability to maintain Hb/hematocrit levels after predonation (55). Although limited in number, there are also studies that have shown the ability of this strategy to increase Hb or hematocrit values and/or avoid transfusions in patients undergoing surgical resection for head and neck carcinoma, (56,57) radical prostatectomy, (58) or gastrointestinal surgery (59–62).

To assist in tailoring treatment and determining whether an individual requires parenteral iron in addition to erythropoietin, baseline laboratory studies may include endogenous erythropoietin level, baseline ferritin level, reticulocyte count, and B12 folate, as well as review of the peripheral blood smear. One should routinely check for occult gastrointestinal blood losses as well as hemolysis. Dosing of erythropoietin has varied widely in surgical studies. In other settings, weekly subcutaneous administration of 40,0000 units appears to be as effective as three-times-weekly dosing regimens (9,63) with a 1.8 g per dL mean increase in Hb during a 16-week community-based study involving anemic patients undergoing chemotherapy (9). If no response has been attained in 4 weeks, one can consider escalating the dose to 60,0000 units as well as adding additional iron.

Darbeopoetin alfa, a novel erythropoiesis stimulating protein, was approved by the FDA in 2001 for the treatment of anemia in patients with chronic renal failure, gaining approval for chemotherapy-induced anemia in 2002. It binds to and activates the same receptor as recombinant human erythropoietin but with a longer serum half-life, having the potential for prolonging dosing intervals. There is limited data to date with its usage in the presurgical setting.

IRON SUPPLEMENTATION

Iron deficiency is frequently seen in the anemic patient with cancer, characterized as being either absolute (depleted iron stores) or functional (iron is inadequate to meet the increased demands of stimulated erythropoiesis) (64). It is estimated that only 50% of cancer patients respond to erythropoietin therapy, (65) with iron deficiency implicated as one of the primary reasons for lack of response. Laboratory measurements for screening and definitively diagnosing iron deficiency include baseline ferritin and transferrin saturation/percentage, both of which are indirect measurements, and the percentage of hypochromic RBCs (a direct measurement) (64). Each 100 mcg of ferritin correlates with 1 g of stored iron. We recommend the addition of iron supplementation in all patients initiating therapy with erythropoietin and utilization of intravenous iron (a) for those who cannot tolerate oral supplementation or (b) if the ferritin level is less than 200 mcg per mL and/or transferrin saturation is less than 20%. One may not wish to exceed 500 mcg per L of ferritin due to concerns of iron overload.

Although there are various oral iron formulations available, most providing approximately 200 mg per day of elemental iron, their use may be limited by both tolerability issues and an inability to meet the demands of accelerated erythropoiesis. Intravenous iron dextran (INFeD) has been associated with small numbers of anaphylactic reactions attributed to the dextran component. Although iron dextran has the advantage of one time total dose infusion, it does require premedication. Two dextran-free preparations have been introduced in the United States in recent years: sodium ferric gluconate (Ferrlecit) and iron sucrose (Venofer). These newer preparations require weekly dosing but are reported to have fewer anaphylactic reactions without associated mortality.

Intraoperative Phase

ANH is an intraoperative blood conservation technique that has been used to reduce allogeneic blood exposure. Other advantages of the technique include avoidance of the waste and high costs associated with preoperative autologous donation and its ability to be used in procedures that cannot be delayed (66). The technique involves the removal of approximately two units of the patient's blood prior to surgery and then replacing this volume with an acellular crystalloid or colloid solution to maintain normovolemia, resulting in a decreased Hb and hematocrit (51). After surgery and when bleeding is under control, the blood is then reinfused. ANH is recommended for patients who are expected to lose more than 20% of blood volume; however, the technique is generally not recommended for those who are anemic at baseline (Hb$\leq$10 mg per dL).

Intraoperative cell salvage also has been utilized to avoid homologous blood transfusions in many surgeries where anticipated blood loss is expected to be significant. Although series in which cell salvage has been utilized during oncologic surgeries have suggested that this is safe without an increase in cancer recurrence, (20,67) the concern remains that the presence of malignant cells suctioned from the operative field may be reinfused and cause metastasis. In fact, the use of intraoperative blood salvage as part of oncologic surgery is considered by some to be contraindicated. Despite these concerns, there is growing experience with the use of intraoperative blood salvage in patients with a wide range of tumor types (68,69). In a study of patients undergoing radical retropubic prostatectomy, the risk of cancer recurrence was assessed among patients who received cell-salvaged blood using a commercial cell saver (n = 87), autologous transfusion only (n = 264), or no transfusion (n = 57) (67). Transfusion had no statistically significant effect on the risk of prostate cancer recurrence based on multiple regression, and a subsequent analysis found that the likelihood of recurrence was lowest in the cell salvage group. Overall, there are no convincing data that intraoperative blood salvage increases the risk of disease recurrence or metastasis in cancer patients, or that it confers an adverse impact on survival (69); however, data from large prospective trials are not available.

Various techniques such as leukodepletion have been utilized in an attempt to eradicate most but not all of the malignant cells that may be present in intraoperatively collected blood. Blood cell irradiation may offer the ability to more effectively exclude malignant cells from the final product. The use of blood irradiation in conjunction with intraoperative autotransfusion has been proposed as an effective method of eliminating contaminating tumor cells and decreasing the risk of systemic dissemination of cancer (68,70,71). This method has generally been shown to be safe and effective for the elimination of malignant cells (71) and does not appear to affect the function and viability of RBCs (68). Further, the reinfusion of irradiated blood does not appear to produce an inflammatory response during cancer surgery (70). Hansen et al. (71) described their successful experience with the use of intraoperative blood salvage plus irradiation in over 700 patients,

demonstrating that approximately half of the RBCs lost during cancer surgery can be salvaged and reinfused (in similarity to experiences in nononcologic surgery) (68). Overall, the practicality of this procedure resides in the access to blood irradiators as well as the ability to incur the increased cost.

Postoperative Phase

Postoperatively, the oncologic surgical population poses an increased risk of bleeding related to thrombocytopenia or coagulopathy. Malignancy itself is also a hypercoagulable state, increasing the risk of perioperative thrombosis. Many patients may have had a thrombotic episode and therefore may already be on anticoagulation.

Underlying coagulopathies may be related to thrombocytopenia, poor nutrition, liver metastasis, uremia with platelet dysfunction, disseminated intravascular coagulopathy (DIC), or chronic anticoagulation for thrombosis. There are multiple causes of thrombocytopenia, which include marrow damage or infiltration by malignancy, ineffective production of platelets because of B12 and folate deficiency related to malnutrition and hypersplenism. Nonimmune-mediated and immune-mediated peripheral destruction of platelets can be associated with drugs, lymphoproliferative disease, or alloimmunization. To manage thrombocytopenia and avoid bleeding, strategies include the use of protein pump inhibitors, stool softeners, and cessation of menses with hormones. For enhancement of hemostasis, various drugs could be utilized such as aminocaproic acid, vitamin K, DDAVP as well as infusion of cryoprecipitate. Thrombopoietin is a drug that could be used during cancer treatment to stimulate platelet recovery.

CONCLUSION

There are multiple benefits to the oncologic patient avoiding transfusion, which include the inherent risk of infection and transfusion reactions, but as important, avoidance of immunomodulation that can lead to cancer recurrence and increased infections in already immunocompromised patients. The oncologic patient may present more frequently to surgery with preexisting anemia as well as an increased risk for bleeding and thrombosis. Aggressive preoperative priming with erythropoietin and iron along with blood conservation techniques should be utilized in the oncologic surgical patient to avoid both anemia and transfusion exposure.

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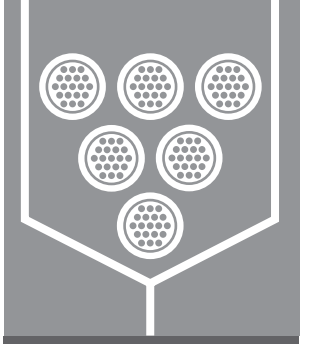

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Transfusion and Coagulation Dysfunction in Neurosurgery

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The basic considerations for coagulation and hemostasis in neurosurgery are similar to that of other surgical subspecialties. However, unlike other surgical subspecialties, most neurosurgical procedures occur within the fixed volume of the skull or spinal canal. This creates a crucial distinction to the procedures of other subspecialties and narrows the margin for error. Dysfunction of coagulation and hemostasis in the neurosurgical setting must be avoided.

Hemorrhage results in mass effect leading to brain or spinal cord compression with potential permanent neurologic injury or death. This concept and the relationship to intracranial pressure (ICP) are well described by the Monro-Kelli Hypothesis. It states that the intracranial contents are normally fixed and consist primarily of brain parenchyma, (CSF), and blood (contained within circulating blood vessels). Because the rigid skull cannot expand, any additional element (i.e. hematoma, tumor, etc.) is present at the expense of one of these three primary components, which causes a neurologic deficit or elevates ICP, impairing cerebral perfusion.

Blood loss limits oxygen-carrying capacity to the central nervous system (CNS). The brain utilizes 15% to 20% of resting cardiac output and is responsible for about 20% of the total body oxygen consumption. It is almost entirely dependent on oxygen and glucose delivery for energy and has limited ability to derive energy from alternative metabolic pathways (1). Therefore, in a setting of physiologic stress, there may be tremendous strain placed on the brain tissue as a result of blood loss and the subsequent ischemia.

It is clear that both the neurosurgeon and the neuroanesthesiologist must have a sound working knowledge of the principles of coagulation and its management. Any uncontrollable intracranial hemorrhage can easily lead to intracranial hypertension and permanent ischemic damage. The optimum management of transfusion issues in neurosurgery may be approached through the understanding of the following topics: mechanisms of hemostasis; cerebral blood flow, oxygenation, and metabolism; managing common neurosurgical clinical scenarios; preoperative planning to limit intraoperative bleeding; intraoperative management of hemostasis; initial screening of the patient including detection of coagulopathic states, and recognizing factors and conditions that may alter normal coagulation states; and special considerations in neurosurgery

Acknowledgments:
We would like to acknowledge the authors of the previous edition, Mick J. Perez-Cruet and Raymond Sawaya, for their contributions to this chapter.

MECHANISMS OF HEMOSTASIS

Hemostasis is a process that involves a complex interaction between the vascular wall, platelets, and clotting factors (2).

There are two interdependent and intimately overlapping arms to the process: (a) the activation of platelets forming a platelet plug, and (b) the subsequent activation of coagulation factors and the coagulation cascade on the surface of the activated platelet. The process begins with the adherence of a monolayer of platelets at a site of endothelial injury and ultimately will produce a cross-linked fibrin clot. This has traditionally been described as three dynamic, overlapping, and self-propagating phases termed primary, secondary, and tertiary hemostasis. Simplified, these phases can be thought of as the platelet phase, the coagulation factor phase, and finally the biochemical remodeling phase.

Primary hemostasis: This initial phase in the coagulation process is marked by the activation and actions of platelets. Platelet recruitment occurs within seconds to minutes of injury to the vessel wall and through platelet adhesion, aggregation, and secretion will result in a platelet plug. The initial step after exposure of endothelium due to vessel injury is the binding of a monolayer of platelets to that site. This is followed by platelet aggregation and activation with concomitant secretion of platelet granules leading to the expression of a fibrinogen receptor on the surface of the now activated platelet. This fibrinogen receptor binds fibrinogen which itself will now link together platelets to form the platelet plug. For platelets to contribute to clotting appropriately there needs to be both normal platelets and a normal platelet environment, i.e., cofactors.

The most notable cofactor is von Willebrand's Factor (vWF). Functional platelet aggregation is dependent upon polymers of von Willebrand factor (vWF). The binding of polymers (not monomers) of vWF with assembling platelets allows aggregation and thus formation of the initial monolayer. Von Willebrand's disease occurs when vWF cannot polymerize, therefore disrupting the formation of the platelet monomer and hence the subsequent plug.

Secreted platelet granules include ADP, fibrinogen, the α-granule, and vWF—already beginning the self-propagating cascade.

Secondary hemostasis: The process of forming a platelet plug will concurrently activate coagulation factors on the surface of the platelet and within minutes to hours initiate the coagulation cascade. This cascade leads to the generation of thrombin and ultimately leads to a fibrin clot. Thrombin generation typically occurs via activation of one of two pathways—both converging on the activation of Factor X and the common pathway. The intrinsic pathway is initiated by plasma coming into contact with a negatively charged surface—either the platelet surface or the exposed basement membrane at the time of injury. The extrinsic pathway is initiated via Factor VII when tissue damage exposes blood to tissue thromboplastin, or more specifically tissue factor (TF), which is released as a result of the injury to the endothelium.

Tertiary hemostasis: The last phase is marked by biochemical reactions serving to strengthen the fibrin clot and then initiate fibrinolysis. This occurs within hours to days with cross-linking of the fibrin clot by Factor XIIIa.

Carr et al. (2) recently proposed a revised three-phase model described as Initiation–Amplification–Propagation. This model emphasizes several features: (a) clotting does not occur sequentially but instead in three distinct but overlapping phases, (b) there is an important interplay between both circulating plasma factors and the cellular components at the site of endothelial injury, and (c) the most important aspect of the enzymatic coagulation cascade may be the generation of thrombin with a successive series of self-propagating reactions resulting in the production of a *thrombin burst.* The fibrin clot may just be a secondary result of this thrombin burst but may not be the primary purpose of the clotting mechanism. Briefly, the three phases are:

Initiation: The mechanism begins with endothelial damage exposing dormant platelets to collagen, vWF, and TF-bearing cells. Platelets are activated both by attachment to collagen and through thrombin generated at the TF site (2). It is the coupling of circulating FVII with TF on the tissue-bearing cell that triggers the process. The result is a modest conversion of FX to FXa and FIX to FIXa.

Amplification: The resultant FXa from initiation will propagate reactions as described traditionally (3) to produce thrombin. Amplification occurs as thrombin interacts with concurrently activated platelets setting off several positive feedback loops. In short, this association will activate FVa, FVIIIa, FXIa and promote both assembly of enzyme complexes and further platelet activation.

Propagation: Again, returning to the concept of plasma factors interacting with tissue-bearing cells, the activated coagulation factors from amplification assemble on the activated platelet surface. Prothrombin (FII) is produced from this interaction and supports still further platelet activation and subsequent fibrin formation. To summarize: the initial modest thrombin generation at the site of tissue damage is amplified in the presence of platelets and then propagated on the surface of activated platelets. The final result is a *thrombin burst* with ensuing activation of platelets leading to the conversion of fibrinogen to fibrin.

The key points to recognize are that the early events of the clotting mechanism involve the actions of platelets and later come to involve the coagulation factors and cascade. Consequently, bleeding within the first 24 hours is likely to be from dysfunction of platelets. Patients who develop bleeding days after surgery will have defects in secondary or tertiary hemostasis (4).

CEREBRAL BLOOD FLOW, OXYGENATION, AND METABOLISM

As mentioned earlier, the brain uses approximately 20% of total body oxygen consumption and receives nearly 15% of resting cardiac output and accounts for only 2% of total body weight. Initial injuries to the CNS are often complicated by a subsequent secondary injury from prolonged ischemic states and poor oxygen delivery to damaged tissues. There are tightly controlled cerebral autoregulatory mechanisms to ensure adequate blood flow, and therefore oxygen delivery, to the brain and spinal cord. Normal central nervous system physiology has inherent distinctions as compared to the rest of the body. These include CSF production, the blood-brain barrier (BBB), and the proportionately high metabolic demands with relatively few options as energy substrates, i.e., oxygen and glucose (5).

The normal brain has a global cerebral blood flow (CBF) of 50ml/100g/minute (6). Gray matter CBF is three to four times greater than white matter and gray matter consumes nearly twice as much glucose and oxygen as white matter (6). Cerebral perfusion pressure (CPP) can be estimated by the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). CPP is the primary stimulus for autoregulatory changes in CBF (6). Cerebral autoregulation simply stated is the maintenance of relatively constant CBF in the setting of vacillating CPP ranging 50 to 150 mmHg. This is accomplished primarily at the vascular level by alterations in smooth muscle tone and vessel diameter. Detailing the numerous mediators of cerebral autoregulation and CBF/Metabolic Coupling would be too cumbersome for this chapter. Suffice it to say that increased metabolic demands are usually matched by increased CBF and this increase in CBF is produced through alterations in vascular dynamics—either smooth muscle tone or through various other mediators that serve a similar ultimate purpose.

Oxygen delivery is a product of CBF and arterial oxygen content, which takes hemoglobin levels into account (6). The management of the injured brain is complex as the autoregulatory mechanisms are likely disrupted. At this juncture the vessels may not be able to adapt in diameter as efficiently and blood viscosity becomes more important in maintaining cerebral oxygenation. In these cases lowering hematocrit from between 45% and 50% to between 30% and 35% will improve CBF while ensuring sufficient oxygen content and delivery. A decrease to <30% would be detrimental as the oxygen-carrying capacity becomes too low to be beneficial (7).

COMMON NEUROSURGERY CLINICAL SCENARIOS

Traumatic Head Injuries

These cases are often complicated by coagulopathy and can offer significant challenges to the clinician. Head trauma is an independent risk factor for disseminated intravascular coagulation (DIC), possibly because the brain is rich in thromboplastin, which may be released into systemic circulation with trauma (11). Patients with traumatic head injuries are almost always suffering from multi-trauma and the subsequent resuscitation can cause a dilutional coagulopathy.

Gun Shot Wounds to the Head

There is a high incidence of death (75% to 80%) with gun shot wounds to the head (12). Most patients with a gunshot wound to the head do not survive to make it to the neurosurgeon (13,14). It is estimated that greater than 90% of patients shot in the head in civilian settings die, and two thirds at the scene of the crime (15). Surgical intervention can be extremely bloody. Frequently, the patient is coagulopathic from blood loss and hemodilution. An emergency type, and cross-match and a coagulation profile should be ordered upon arrival. Fresh frozen plasma and platelets should be available intraoperatively. Not infrequently, a fresh frozen plasma drip is started once the patient enters the operating room to improve coagulation.

Neurogenic Shock Due to Head Trauma

In addition to spinal cord injury, neurogenic shock can occur in the setting of head trauma with acutely elevated intracranial pressure (16). Patients with neurogenic shock after a head injury are often treated using volume expanders such as whole blood, plasma, or crystalloid with or without vasoactive drugs. The efficacy of blood transfusion therapy has been questioned because animal studies have shown these products to be detrimental in the treatment of neurogenic shock due to brain injury (17). Rahimifar et al. (17) found that in the absence of hypovolemia, neurogenic shock due to raised intracranial pressure should be treated with dopamine and normal saline infusion but not blood transfusion. Transfusion of whole blood, packed cells, or plasma failed to improve hypotension due to neurogenic

shock resulting from head injury and in fact caused further deterioration in the blood pressure. Because of neurogenically induced cardiac failure, they believed that blood transfusions may result in additional stress on the failing heart caused by increased cardiac preload.

Stab Wounds to the Head

Penetrating stab wounds to the brain can be best described as low-velocity wounds with a small area of impact. As many as one third of these patients will have a vascular injury (18). Angiography is used to delineate vascular injury such as traumatic aneurysms, which occur in 12% of patients (19).

Dural Sinus Injuries

Lacerations of the dural sinuses can result in copious blood loss. The first step to controlling dural sinus lacerations is to gain an adequate exposure. This may involve tamponading the area with Gelfoam and a cottonoid while removing additional bone. Placing temporary clips can be helpful in controlling dural sinus lacerations; however, placing clips blindly may lead to further tearing of the sinus. Additionally, coagulation usually leads to increased bleeding because the dura shrinks away, widening the laceration. A Foley catheter tip can be inserted into the sinus and the balloon inflated to occlude the sinus while a bypass or graft is fashioned. However, most supratentorial sinuses, unless occluded slowly by a meningioma, cannot be occluded acutely without considerable risk (20). Additional techniques include primary closure of the laceration using a running suture; application of pericranium or fascial grafts; or the application of muscle, Gelfoam, or avitene to small dural lacerations. Raising the patient's head will help to reduce venous pressure and bleeding from a torn sinus.

Scalp Injuries

The scalp is vascular and seemingly minor lacerations can result in possible life-threatening blood loss. Therefore, it is imperative that the patients who present with head trauma are adequately examined for scalp injuries. Injury to the superficial temporal or occipital arteries can result in hemodynamic instability and shock from blood loss. In patients with thick hair, shaving the head over the injured area is necessary to adequately examine the wound. Infants with cephalhematomas or blood located between the galea and skull can lose a significant blood volume. Cephalhematomas present with asymmetric swelling of the head and increase in frontal occipital circumference after head trauma. In these cases, the hemoglobin and hematocrit levels should be checked frequently.

Spinal Cord Injury

The rate of spinal cord blood flow does not differ significantly from cerebral blood flow; however, after spinal cord injury, animal models have shown a decline in the rate of spinal cord blood flow (21,22). This decline is thought to be due to a loss of autoregulation at the level of injury (23,24). A number of studies have investigated methods of reducing posttraumatic ischemia after spinal cord injury by improving spinal cord blood flow using whole blood transfusions and dextran (25). Although some studies have shown red blood cell transfusion is effective in reversing the post injury hypotension by doubling the spinal cord blood flow rate (26), other studies using whole blood transfusion failed to show an increase in spinal cord blood flow. This lack of efficacy in the later case was explained on the basis of hemoconcentration (25).

Intracerebral Hemorrhage

Arterial hypertension accounts for 50% to 90% of spontaneous intracranial hemorrhages (ICHs) (27) with a high percentage (90% to 92%) of nontraumatic thalamic and putaminal hemorrhages are believed to result from hypertension (28). Likewise, most cerebellar hemorrhages (86%) result from hypertension (29). The 30-day mortality rate for ICH is 40% to 50% (30). Predictors of poor outcomes include advanced age, poor neurologic status at presentation, larger hematoma size, intraventricular extension of hemorrhage, use of anticoagulants, and brainstem location (30). The primary mechanism of hypertensive ICH is thought to result from chronic arterial hypertension with high-velocity blood flow passing abruptly, often at perpendicular angles, into smaller and deeply perforating branches of lateral lenticulostriate arteries. The so-called Charcot-Bouchard microaneurysms form as a result of fibrinoid necrosis of the vessel wall and rupture at this point may cause some ICHs. Antihypertensive therapy is effective at reducing the incidence of spontaneous ICH and recurrent hemorrhage (31,32). No effective treatment has been devised for ICH and still remains largely medical and supportive. However, management strategies in the acute setting of ICH are evolving. Recent data have show that 38% of hematomas increase by more than 33% within 20 hours (30). As a result, the current recommendation is to maintain MAP $<$130 immediately following the hemorrhage but this value is a topic of ongoing debate. Surgical management has not been proven to improve outcomes in cases not involving the cerebellum or impending herniation (30). The recent International Surgical Trial In Intracerebral Hemorrhage (STICH trial) (33) compared early surgical evacuation versus medical management failed to show

any advantage for surgical management. Critics of the study argue that it contained intrinsic bias as patients were only randomized when the surgeon was uncertain of the best treatment. Furthermore, patients that deteriorated in the conservative arm crossed over to the surgical arm (34). More studies will surely be devised as a result of this important paper.

Only a relatively low percentage (7.8%) of spontaneous intracranial hemorrhages are secondary to hemostatic disorders, coagulopathies, or the use of anticoagulants although incidence is rising (35–38). However, it is these cases that must be recognized without delay in order to maximize patient outcome. The annual risk of ICH in patients on anticoagulant therapy is 0.3% to 1.1% (30). Outcomes are worse in these cases with 30-day fatality rates from 44% to 68% (30). It is commonly agreed that anticoagulant-associated intracerebral hematomas (AAICH) present with larger hematoma size and are more likely to grow and cause neurologic deterioration. Hypertensive ICHs have well described regions of the brain in which they occur. It is still uncertain if AAICHs have a similar predilection although early studies suggest a greater tendency for lobar hemorrhages. Management is focused on rapid reversal of coagulopathy with agents such as Recombinant Factor VII, intravenous Vitamin K, and FFP.

Cerebral Aneurysms and Vascular Malformations

Another common neurosurgical problem is ruptured vascular lesions. Until definitive treatment can be attained, initial efforts should be directed toward minimizing initial ischemia after hemorrhage and preventing further injury from vasospasm and/or rehemorrhage. The most common cause of subarachnoid hemorrhage is a ruptured cerebral aneurysm. The amount of blood in the basal cistern within 4 days after a spontaneous subarachnoid hemorrhage, as seen by head computed tomography (HCT), is a good predictor of the severity of symptomatic intracranial cerebral vasospasm (39). Generally speaking, the larger the blood load, the higher the ICP, the lower the CPP and CBF, and the greater the loss of autoregulation. Patients with ruptured aneurysms develop a reduction in circulating blood volume, and treatment is directed at restoring, or elevating, blood volume to reduce symptomatic vasospasm (40–42). Ischemic symptoms due to cerebral vasospasm after subarachnoid hemorrhage have been alleviated using intravascular volume expansion by blood transfusion, induced hypertension, increased cardiac output, and plasma expanders—the so-called HHH Therapy (43–46). The goal of this therapy is to improve regional cerebral oxygen delivery and therefore limit ischemic damage secondary to vasospasm. Autoregulation appears to be impaired in cerebral vasospasm after subarachnoid hemorrhage, and therefore cerebral blood flow in the ischemic brain is volume, pressure, and flow dependent (40,47–49). Protocols for treatment of vasospasm include intravascular volume expansion with whole blood or packed red blood cells, supplemented with plasma fractionate or albumin (50). Some neurosurgeons have advocated giving at least 400 mL of whole blood immediately after clipping a cerebral aneurysm even after conservative blood loss (51). These authors have reported improved clinical outcome and reduced symptomatic vasospasm after early blood transfusion at the time of operation (51,52). Pritz et al. (45) reported a decreased incidence and severity of neurological deficits associated with postoperative vasospasm in patients who were *over transfused* with 1 to 2 units of whole blood after aneurysm clipping. Therefore, they postulated that intraoperative volume depletion might play a role in vasospasm, particularly during the immediate postoperative period. Others have found that depleted red blood cell volume was more responsible for neurological deterioration than was a lowered plasma volume in patients with cerebral vasospasm after subarachnoid hemorrhage (51). Complications can occur with overtransfusion of patients with vasospasm, and therefore it is important to determine that neurological deterioration is due to brain ischemia secondary to anemia and hypovolemia. Postoperative extradural hematoma has been reported in a patient receiving hypertensive therapy including blood transfusion for delayed cerebral ischemia after aneurysm clipping (53). In addition, hyponatremia, pulmonary edema, and coagulopathy can result from HHH therapy, (50) leading to mental status changes. A marked increase in hemoglobin concentration can result in decreased blood viscosity and slugging, leading to infarction when vasospasm exists. In the unclipped aneurysm patients, this therapy can result in rerupture of the aneurysm. To ensure that neurological deterioration is secondary to vasospasm, serum electrolytes, electrocardiogram, chest x-ray, and head computed tomography should be checked if acute deterioration is noted. In addition, noninvasive techniques such as transcranial Doppler can predict the severity of vasospasm based on cerebral blood flow rate.

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Osler-Weber-Rendu disease is an inherited autosomal dominant disorder characterized by angiodysplasia, including cerebral arterial venous malformations (54). These arteriovenous malformations can rupture, resulting in ICH. No specific treatment for this condition is currently used.

CNS Neoplasms

Intracranial Neoplasms

The incidence of spontaneous ICH from brain tumors has been reported to be 1.3% to 9.6% (55). There appears to be a correlation between tumor pathology and hemorrhage rates. Realization of possible tumor pathology based on clinical presentation, imaging techniques, and location of tumor before starting an operation can prepare the surgeon to take steps to minimize blood loss and the need for blood transfusions. Those tumors found to have the higher degree of hemorrhage include metastatic melanoma (50%), mixed oligodendroglioma/astrocytomas (29.2%), and sarcomas (56). Tumors that are frequently associated with spontaneous hemorrhage include glioblastoma (57–59), tumors of neuroepithelial origin, oligodendroglioma, (60) and renal cell carcinoma metastasis. Even though these tumors have a tendency to bleed spontaneously, their bleeding can generally be controlled during surgery. Additional tumor types that are prone to intratumoral hemorrhage include choriocarcinoma (61,62), metastatic tumors, (63) and pituitary adenomas (55). In contrast, meningiomas have a low rate of spontaneous hemorrhage; however, their resection can be bloody. A series of 310 cases of meningiomas reported only four having spontaneous hemorrhages (55). Intraoperative hemorrhage from meningiomas can be reduced by preoperative embolization and/or intraoperatively by initially coagulating the vascular pedicle to the tumor. Factors that may increase tumor hemorrhage rate include age, with children having a higher incidence of hemorrhage, (55,64) and changes in intracranial pressure after placement of ventricular drainage, particularly in patients with posterior fossa tumors (65). Interestingly, hypertension and anticoagulant therapy do not appear to increase the incidence of spontaneous tumor hemorrhage (56).

Spinal Metastasis

Metastatic spinal tumors usually occur in individuals over 50 years of age and are more common in men than in women. In a series of 250 malignant extradural tumors, 68% were metastatic (66). Metastatic spinal neoplasms can be highly vascular, making resection difficult and bloody. Those metastatic tumors that are particularly vascular include renal carcinoma, thyroid carcinoma, and melanoma, which comprise roughly 9%, 6%, and 2% of metastatic tumors to the spine, respectively (67). As described in a previous section, preoperative arteriography and embolization of feeding vessels can significantly reduce intraoperative blood loss and enhance the ability to safely resect these lesions.

Spinal Hemangiomas

Spinal Hemangiomas are also known as vertebral hemangiomas, or hemangiomatous angioma. These are benign tumors of the spine characterized by the replacement of normal bone marrow with blood vessels. Rarely do they cause neurologic compromise or pain—but definitive treatment in these incidences can pose a difficult problem to the surgical team. Mass effect from spinal hemangiomas can come from epidural growth of the tumor, expansion of the bone, compression by vessels, compression fractures, spontaneous hemorrhage, or spinal cord ischemia (68). Surgical management is reserved for those lesions causing neurologic deficit and sometimes for pain alone. Due to the highly vascular composition of these tumors, careful preoperative planning is required to minimize hemorrhage during resection. Surgical adjuncts include embolization and radiation therapy. The treatment strategy of choice when possible is preoperative embolization, subtotal versus total resection, and postoperative radiation. Part of the radiographic workup for symptomatic lesions should include spinal angiography. Preoperative embolization is useful in cases where the feeding vessel does not also supply the anterior spinal artery.

Amyloid Angiopathy

In cerebral amyloid angiopathy, amyloid beta protein is deposited in the walls of leptomeningeal and cortical arteries as well as arterioles (69). Because the arterial walls are weakened, spontaneous ICHs can occur in normotensive patients with cerebral amyloid angiopathy (70–72). These hemorrhages may be multiple, recurrent, and tend to be lobar in location (73,74). The hemorrhagic diathesis may be caused by factor X activity, platelet dysfunction, or fibrin polymerization (75,76). Neurosurgical evacuation of ICH in older individuals in poor neurological condition results in high mortality and morbidity, and therefore treatment should be restricted to supportive measures (77). Leblanc et al. (77) also recommend delayed surgery in patients in good condition, with meticulous attention to hemostasis to avoid rebleeding. Although there is no specific treatment for amyloid angiopathy, treating an underlying disorder such as chronic infection or dysproteinemia can be helpful (78).

Anticoagulant Use

In a large sample size of patients 40 years or older, the prevalence of spontaneous intracranial bleeding while on high intensity anticoagulant therapy (INR 3.0 to 4.5) was 6.7% (79). This same study found that the highest rate of ICH occurred within the first year of treatment. Excessive anticoagulation has been associated with an increased risk of spontaneous cerebral hematoma (80,81). As a result a more conservative range of 2.0 to 3.0 is more commonly recommended and only has an annual bleeding risk of 0.3% to 1.1%.

Heparin

Heparin is used for acute short-term anticoagulation and works by binding to antithrombin III. Heparin then potentiates the inhibition of thrombin activity, resulting in reduced conversion of fibrinogen to fibrin. Its action can be reversed with protamine. Heparin drips are generally stopped 4 to 6 hours prior to a procedure. Intracranial hemorrhages are the most common cause of fatal bleeding from anticoagulation therapy.

One must also be aware of Heparin-Induced Thrombocytopenia (HIT) and Heparin-Associated Thrombus (HAT). HIT comes in two forms and occurs in up to 5% of patients receiving unfractionated heparin. *Type 1 HIT* only causes a transient decrease of platelets in the first week of its use and corrects without intervention. *Type 2 HIT* is more severe and is the result of the formation of an antibody to a complex composed of heparin and a normal platelet protein. The product of this antibody interaction is platelet activation and thrombocytopenia. In a small subset of these patients the platelet activation will be excessive and cause a massive thrombosis termed HAT. Any patient developing thrombus while on heparin should be considered to be at risk for HAT—even in the face of a normal platelet count (82).

Coumadin

Coumadin is given parenterally for long-term management of anticoagulation. It acts as a vitamin K antagonist by inhibiting the carboxylation of terminal glutamic acid residues of factors II, VII, IX, and X in the liver and reduces the plasma levels of proteins C and S. The risk of ICH is increased sixfold to 11-fold in patients taking oral anticoagulants compared with the general population (83,30).

Use of Antiplatelet Drugs

Generally, all these agents either directly or indirectly interfere with platelet function. A platelet has a half-life of 7 days, so ideally patients should stop taking any antiplatelet medication 7 days prior to any procedure in order to allow a new population if platelets to be produced.

Aspirin: Acts by reducing platelet aggregation, which may cause blood oozing during surgical procedures. More routine procedures may be safe after just 2 to 3 days off aspirin as the buildup of functional platelets in this time frame is likely sufficient to provide adequate hemostasis. For larger procedures the recommendation is to stop aspirin 5 days prior to surgery and operate on the sixth day.

Plavix and Ticlid: are agents that prevent continued stimulation of platelets through inhibition of ADP-induced activation of platelets.

ReoPro, Aggrastat, and Integrillin: are all drugs that block platelet aggregation by binding to the platelet fibrinogen receptor and act as anti-GPIIb-IIIa antibodies.

Epsilon-Aminocaproic Acid: Epsilon-aminocaproic acid is an inhibitor of fibrinolysis and has been used to prevent rebleeding from ruptured cerebral aneurysms by preventing clot dissolution (84,85). However, at higher doses, hemostatic studies have shown that epsilon-aminocaproic acid may actually increase the risk of bleeding by interfering with platelet function (86). Glick et al. (86) recommended that doses should not exceed 24 g per day and that patients should be evaluated with serial bleeding times to ensure normal platelet function. If the bleeding time is prolonged, the dosage should be lowered or the drug discontinued.

Vitamin K Deficiency

This condition is probably often overlooked in patients. It will characteristically develop in an ICU patient subjected to malnourishment from being made NPO or exposed to antibiotic use. Anytime an inpatient develops a prolongation in PT one should think of vitamin K deficiency. Treatment would be with oral Vitamin K.

Cocaine Abuse

Cocaine abuse is associated with a variety of CNS complications, including subarachnoid hemorrhage, vascular spasms, ICH, stroke, and possibly vasculitis (87–89). Jacobs et al. (90) showed that most patients with radiographic abnormalities and cocaine abuse had ischemic complications. The mechanisms for cocaine-induced cerebral ischemia may involve vasospasm (91–93) or cerebral vasculitis (94). In addition, cocaine can affect hemostasis, leading to cerebral thrombosis due to enhanced platelet aggregation (95). Cocaine has been shown to affect arachidonic acid and thromboxane (95) and deplete antithrombin III and protein C (95).

Sickle Cell Disease

Neurological complications in sickle cell disease occur in 6% to 34% of cases (96,97). Of these cases, 75% are cerebral infarctions (98) with ICH being the second most common cerebrovascular complication estimated to occur in 2.7% to 20% of cases (99,100). The preoperative management of patients with sickle cell disease undergoing craniotomy includes exchange transfusion with washed red blood cells, which reduces the proportion of hemoglobin S (101). Transfusion therapy has also been found to reduce the recurrence rate of stroke in patients with sickle cell disease (102).

PREOPERATIVE PLANNING

Expected Blood Loss

Elective Laminectomy

For an elective laminectomy, a type and screen can be ordered rather than a type and cross-match, which will help to reduce cost and waste. In the type and screen, the patient's red cells are typed for ABO-Rh and the serum is screened for irregular antibodies and is 99.99% compatible (103,104). In a study of 10,000 patients undergoing one-level or two-level laminectomy in community hospitals, 6.7% of patients with uncomplicated hospital stays received a blood transfusion. There was a significantly higher rate of blood transfusion (24%) in those patients having a complicated hospital stay (105). Sarma (106) found that in most patients needing a blood transfusion, after only a type and screen was ordered, there was sufficient time for the blood bank personnel to cross-match the units before transfusion was started. In the remaining three cases not cross-matched before receiving blood, no blood incompatibility occurred. The advantage of type and screen as opposed to type and cross-match is that units of blood are not withheld for a specific patient, resulting in these units becoming outdated and discarded. On average, 2 to 3 units of blood were requested for each elective laminectomy (106). In a review of the literature, Sarma (106) reported that only 240 of 1,512 (16%) laminectomy cases cross-matched for blood actually required blood transfusion. Communication between blood bank personnel and surgical staff was the most important factor in reducing cost and waste by ordering a type and screen rather than a type and cross-match for elective laminectomies.

Elective Craniotomy

In addition, some advocate type and screen for craniotomies because the ratio of used units cross-matched versus actual units transfused is unacceptably high in most institutions. Generally, for every five units of blood ordered for elective craniotomies, only one unit is used (107). Type and cross-match would be indicated in vascular neurosurgical cases such as aneurysm or arteriovenous malformation surgery.

Emergent Surgery

In emergent neurosurgical procedures such as severe head injury, patients should have a type and cross-match performed upon arrival in the emergency room. Typically, these patients have already lost significant blood volume. Patients with scalp lacerations can lose many units of blood due to the highly vascular nature of the scalp. Indeed, patients may arrest from blood loss due to improper attention to scalp lacerations. In addition, trauma neurosurgery is bloody because of the urgency needed to evacuate an intracranial mass lesion or because of the trauma-induced coagulopathic state of the patient. Complete hemostasis is often difficult, and large scalp and bone flaps add to the blood loss. These patients are often coagulopathic from dilution of clotting factors or develop trauma-related DIC. To replace clotting factors, fresh frozen plasma can be given and a fresh frozen plasma drip maintained during the operative procedure. Additional neurosurgical emergencies that would require immediate type and cross-match for blood include ruptured cerebral aneurysm or arteriovenous malformation, removal of spontaneous ICH, and emergent pediatric neurosurgery.

Neuroradiographic Appearance of Coagulopathies

Computed tomography has been helpful in defining those patients that may have an underlying coagulopathy associated with an ICH. A *fluid-blood level* in acute ICH is moderately sensitive in predicting the presence of a prolonged PT or PTT (108). Fluid-blood leveling within an intracerebral hematoma seen in coagulopathy is the result of insufficient clot formation resulting in large quantities of free serum (108–110). Pfleger et al. (108) reported a series of 199 cases of acute ICH. In 9% of the cases, imaging studies showed a fluid-blood layering in the hematoma. Of these cases, 82% had laboratory evidence of systemic coagulopathy with a prolonged PT or PTT. Identifying these patients earlier and before performing surgery can allow correction of the coagulopathic state and reduce mortality rates, which are estimated at 40%. Additionally, localized coagulopathy after traumatic brain injury has been documented, resulting in clotting abnormalities not manifested by prolongation of PT or PTT (111). In these patients, the radiographic fluid-blood layering may be the only evidence of a coagulopathic state. In contrast, patients with thrombocytopenia maintain fibrin mesh formation within the clot, and therefore fluid-blood layering is not seen (112).

Perioperative Measures to Decrease Blood Loss

Cerebral Embolization

Remobilization techniques to reduce intraoperative blood loss from vascular lesions are becoming increasingly more popular as refinements of this technique develop. Cerebral lesions that are frequently embolized before surgical resection include arteriovenous malformations, meningiomas, and metastatic tumors (113–116).

Guglielmi coils are flexible and thus easy to manage. By occluding major feeding vessels to arteriovenous malformations or tumors, the intraoperative blood loss can be

significantly reduced. An additional advantage of platinum coils is that they can be removed and repositioned during the embolization procedure if their placement is not believed to be optimal.

Particulate material used for embolization has the advantage of conforming to the shape of the vessel lumen to achieve complete occlusion. Isobutyl-2-cyanoacrylate has been used for the preoperative embolization of cerebral arteriovenous malformations (116). Other embolization agents include gelatin, polyvinyl alcohol sponge, and microballoons. Microfibrillar collagen, another occlusive agent, has a small particle size and causes occlusion of vessels ranging in size from 20 to 500 μm and thus may limit formation of collateral flow (117,118).

Spinal Embolization

Surgery for spinal tumors can result in significant blood loss requiring blood transfusion. The role of spinal angiography for spinal hemangiomas was already discussed earlier in the chapter. The resection of metastatic renal cell carcinoma and large sacral tumors is usually bloody, which limits their resection. Preoperative percutaneous arteriolar embolization can reduce the rate of blood loss and improve the ability to resect spinal tumors (118). Broaddus et al. (119) reported on six patients who underwent this technique preoperatively. The tumors included metastatic renal carcinoma, metastatic thyroid carcinoma, metastatic melanoma, and giant cell tumor of the sacrum. The embolization technique used microfibrillar collagen, which allowed embolization of small feeding vessels, preventing collateral flow to the tumor. In seven of nine procedures performed on these six patients, the estimated blood loss ranged from 400 to 800 mL and no blood transfusion was given. Without embolization, blood loss can range from 1,500 to 3,000 mL or greater (119).

Correcting Coagulopathies

Traditional methods of correcting coagulopathies are mentioned below. However some of these agents can take hours to become effective making them impractical for use in many neurosurgical cases. However, a new hemostatic agent with essentially immediate onset is becoming available—it is Recombinant Factor VIIa (rFVIIa).

Protamine Sulfate: used to quickly reverse the effects of heparin. In less emergent situations, heparin can simply be stopped 4 to 6 hours prior to the procedure.

Vitamin K: Used to correct coagulopathies from coumadin usage. A patient can be reversed overnight with the administration of oral Vitamin K—subcutaneous route may be too unpredictable. Intravenous use can be used in more urgent situations as long as one is aware of the small potential of allergic reaction. With elective procedures in patients highly dependent on anticoagulation, they can be admitted 2 to 3 days prior to surgery and started on a heparin drip. If they are not as exquisitely dependent on anticoagulation it can just be stopped 4 to 5 days prior to surgery.

FFP: given to replete all clotting factors and treats any plasma protein deficiency.

Cryoprecipitate: given predominately for repletion of fibrinogen in DIC. Also contains Factor VIII and VWF. Especially useful in that will not cause excess volume overload.

DDAVP: has been shown to increase VWF and Factor VIII, most often in Von Willebrand's Disease.

Estrogens: also increase VWF.

Antifibrinolytics: Amicar and *Aprotinin* can be used in bleeding states that are marked by hyperfibrinolysis. However their use is limited because it is often difficult to clinically detect a hyperfibrinolytic state and they have been shown to cause thrombosis.

Prothrombin Complex Concentrates: this contains all the Vitamin K dependent coagulation factors (II, VII, IX, X). Its use has become somewhat restricted due to its excessive thrombogenic qualities.

Recombinant Factor VIIa (rFVIIa): Recombinant Factor VIIa (rFVIIa) is the first recombinant activated clotting factor to receive FDA approval as a hemostatic agent. Its currently approved use is only for bleeding in hemophilia A and B patients who have developed antibodies to factor VIII or IX. Despite this narrow indication literature searches reveal that rFVIIa has been used in a variety of off-label cases to correct coagulopathies. There is an increasing interest in the neurosurgery as recent papers have shown it to: (a) immediately reverse excessive Warfarin coagulopathy, (b) correct coagulopathies of several etiologies allowing immediate neurosurgical procedures, and (c) reduce hematoma growth in spontaneous intracerebral hemorrhages (120). Studies quote a wide dosage range anywhere from 40 to 160 μg per kg. It is a promising drug still under investigation with several current trials exploring its most effective usage, dosage, and specific indications. The primary concerns with its use include cost, mild increase in thrombogenic events, and both uncertain mechanism and dose range. rFVIIa is thought to have near instantaneous onset of action with attainment of hemostasis within 10 minutes (121). Its half-life is relatively short at 2 to 3 hours and indications for repeated doses are not clear although it is clear that a patient's labs need to be followed closely after administration. As stated above its exact mechanism

of action remains controversial. Traditionally, blood-borne endogenous FVIIa will bind to TF-bearing cells upon endothelial injury (TF is not exposed until endothelial injury). Upon binding to TF, the FVIIa–TF complex will then activate the conversion to FX to FXa and FIX to FIXa. The activated FIXa will then bind with FIIIa on activated platelets further promoting cleavage of FX to FXa. It is from the activation of FXa that thrombin is generated, platelet activation is amplified, and the thrombin burst is generated marking the true engagement of the clotting mechanism. But recall that rFVIIa is effective in hemophiliacs who do not have either FVIII or FIX depending on the type. Because of this, some propose that rFVIIa also is capable of directly activating FX to FXa on activated platelets thus bypassing the need for FVIII or FIX (121).

INTRAOPERATIVE MANAGEMENT

Measuring Cerebral Blood Flow

The electroencephalogram (EEG) is useful in monitoring changes in cerebral blood flow during neurosurgical procedures such as carotid endarterectomy. Slowing of the EEG pattern has predictive value in the neurological outcome of patients (122). The EEG becomes slower when the cerebral blood flow drops below 20 mL/100 g/min^{-1} and becomes flat at or below 15 mL/100 g/min^{-1} at a temperature of 37°C. Blood flow below 15 mL/100 g/min^{-1} can result in irreversible neurological damage to the brain. The total mean cerebral blood flow in humans is about 50 mL/100 g/min^{-1}. However, there are variations between the blood flow of the gray and white matter, which are about 80 mL/100 g/min^{-1} and 20 mL/100 g/min^{-1}, respectively. Auto regulation of cerebral blood flow allows changes with varying levels of local metabolic activity.

Spinal cord blood flow is similar to cerebral blood flow, with mean blood flows greatest in the lumbar region followed by the cervical and then the thoracic area (123).

A number of methods have been devised to measure cerebral blood flow, including radioactive xenon clearance. This method is based on the principle that the rate of xenon uptake and/or clearance is proportional to the blood flow in the tissue. The use of this radioactive tracer allows direct monitoring of tissue clearance by external detection using computed tomography. More recently, noninvasive techniques such as Transcranial Doppler and magnetic resonance angiography with phase-contrast pulse sequences have been used to measure cerebral blood flow.

Hemostatic Neurosurgical Instruments

The feature that most distinguishes neurosurgery as a specialty is control of hemorrhage without a ligature (124). The use of thermal energy to achieve hemostasis dates back to the time of ancient Egypt, where papyrus papers give reference to the use of cautery to achieve hemostasis. Galen also popularized the use of cautery. In the modern era, Cushing (125) popularized its use with electrocoagulation; currently, it is the most widely used form of hemostasis in neurosurgery. The advantage of electric cautery is that it causes tissue damage and hemostasis via induction, affecting a much smaller surface area than conductive cautery.

The *Bovie electric scalpel* can be used on a cutting mode, which makes a precision cut while coagulating the tissue, or on coagulation mode, which cauterizes a larger surface area. It is effective in removing or cutting soft tissues while maintaining hemostasis.

Greenberg first developed the bipolar electrocautery in 1945. It delivers a more precise induction current between the two tips of a forceps. It is effective in stopping bleeding from individual vessels or in a small working area such as at the bottom of a spinal incision or deep within the brain. Because it is a forceps, it can be used to place hemostatic agents such as Gelfoam or a cottonoid in the area of bleeding and coagulate at the same time. It is perhaps the most widely used instrument in the neurosurgical arena because of its versatility.

Lasers have been used to assist with removal of tumors while maintaining hemostasis. Lasers cause hemostasis by exerting a thermal reaction with the tissue through excitation of rotational and vibrational qualities of matter (126). The neodymium:yttriumaluminum-garnet laser causes its heating and coagulation effects by preferential absorption by heme-pigmented tissue, long extinction length, and decreased tissue absorption (126).

Hemostatic Agents

Cushing introduced the first absorbable hemostatic agent to neurosurgery in 1911 by using skeletal muscle to stop capillary oozing (127).

Collagen-Derived Material

Microfibrillary collagen (Avitene; Avicon, Inc., Fort Worth, TX) is a fibrous web-like material. It is a water-insoluble natural collagen, consisting of fibers containing microcrystals made from purified bovine dermal collagen (128). Its mode of action is to provide a surface to which platelets can adhere, thereby accelerating platelet-mediated clot formation (129–131). Naturally, this makes it less effective in thrombocytopenic states. It can be effective in treating lacerations of venous sinus that tend to bleed profusely and

more briskly if coagulated. This material was more effective in treating sinus tears than Gelfoam soaked in thrombin (132). An excellent hemostatic agent, animal studies have shown this material to be safe and absorbed rapidly by inflammatory cells (133,134). Resorption of collagen material is done principally by macrophages but also by granulocytes, which both contain collagenase (135).

Oxidized Cellulose

Oxidized cellulose (Surgicel, Johnson and Johnson, New Brunswick, NJ; or Oxycel; Parke-Davis, Morris Plains, NJ) is an absorbable fabric consisting of cellulose in the form of cotton, gauze, or paper that is subjected to oxidation by nitrous oxide (136). The mechanism by which oxidized cellulose produces hemostasis is dependent on a chemical reaction. The major use of oxidized cellulose is to control blood oozing from broad surfaces such as the dura or brain surface. It is also used effectively in spinal operations for bleeding from the spinal cord where electrocautery hemostasis could lead to spinal cord damage. An advantage of oxidized cellulose is its bactericidal activity that has been shown to affect over 20 pathological organisms (137). The bactericidal effect is caused in part by the acidic pH and can be reversed with base (138). The tissue reaction to oxidized cellulose is mild and does not delay wound healing (139). The rate of absorption varies from 2 days to 6 weeks depending on the amount of agent used, the amount of blood present, and the degree of oxidation (140,141). Note that some references site that excessive amounts left at the surgical site may retard bone growth (142).

Gelatin Foam

Gelatin sponge (Gelfoam, Upjohn Co., Kalamazoo, MI) is an absorbable gelatin material that has been specifically treated. It was first introduced in 1945 by Correll and Wise (143). Neurosurgeons frequently use Gelfoam because of its ease of application and hemostatic qualities. Typically, the Gelfoam-soaked sponge is used by first compressing the sponge to squeeze out excess thrombin, improving the hemostatic ability of the sponge, and then applying it to the wound and covered with a cotton pledget. A sucker is then applied to the cotton pledget. The sponge can be removed after 10 seconds or left in place. The gelatin sponge itself has no inherent hemostatic action, but after the addition of topical thrombin, it becomes an effective hemostatic agent. The pressure of the blood-soaked sponge and the large surface area produced by the pores in the sponge control oozing via a tamponade effect. However, because of the sponge's ability to absorb blood and expand, it should not be left in place in confined areas such as the spine where expansion could lead to nerve root or cord compression. Studies have shown that the gelatin sponge material is usually absorbed completely within 20 to 45 days after implantation (144,145). Because it is a foreign material, if left in place, it can increase the incidence of wound infection (146–148). There are a number of neurosurgical applications for the gelatin sponge. It is effective at controlling capillary bleeding from the brain. In spinal surgery, it is frequently used to control bleeding from the venous plexus during laminectomies. It has been used to control bleeding from cancellous bone during bone fusion and was found to reduce bleeding by 61% to 75% over control values (149,150); at the same time, the gelatin sponge does not retard bone healing (149). Gelatin paste made by mixing 1 g of gelatin powder with normal saline was found to be more effective at controlling bone bleeding than Gelfoam (149,151). The gelatin sponge is also effective at controlling venous sinus bleeding with no evidence of intravascular thrombus formation (148). In addition to its hemostatic applications, the gelatin sponge has also been used to repair dural defects and can be effective at sealing cerebral spinal fluid leaks (144). No significant difference in tissue reaction was seen in comparing brain tissue reaction with microfibrillar collagen and gelatin foam in canine brain lesions (152).

Hydrogen Peroxide

Hydrogen peroxide produces a chemical hemostasis and is used by soaking cotton balls in 3% hydrogen peroxide. The soaked cotton balls are then packed into the oozing brain cavity and left in place for 5 minutes to produce hemostasis. The cotton ball is then gradually removed while irrigating slowly. Although using hydrogen peroxide on the brain is not encouraged by all neurosurgeons, no detrimental effect has been noted (153). This technique is especially effective in managing the oozing after evacuation of an intracerebral hematoma. Because of the expansion of hydrogen peroxide on exposure to blood, it should be instilled with caution in confined areas such as the subdural space to avoid brain compression (153). In addition to its hemostatic qualities, it also acts as a bactericidal agent.

Bone Wax

Invented by Horsley in 1892, bone wax has no adherent hemostatic properties. Bone wax prevents bleeding by its tamponade effect on bone bleeding (154).

Thrombin

Mellanby (155) first described the laboratory preparation of thrombin in 1933. Thrombin is a protein produced via a reaction in which bovine prothrombin is activated to thrombin by tissue thromboplastin in the presence of $CaCl_2$ (132). It is supplied as a powder and is made into a solution with

normal saline. A commonly used and effective material for carrying thrombin is the gelatin sponge. Thrombin can be applied topically to control capillary oozing during operative procedures and has been found to shorten bleeding from puncture sites in heparinized patients (139). Thrombin begins to lose its activity within 8 hours at room temperature and within 48 hours if refrigerated (127). It has been noted to cause edema when placed on brain with disrupted pia (142).

Fibrin Glue

Fibrin glue is a topical hemostatic agent prepared by combining fibrinogen with thrombin to create a biological adhesive. Although commercial preparations are available, autologous fibrin glue carries less risk of transmitting infection. Fibrin glue is obtained from preparing cryoprecipitate from plasma obtained either from plasmapheresis or harvested from a unit of predonated blood (156). Fibrin glue has a number of applications in neurosurgery including controlling blood oozing; adhering muscle or fascial dural patch grafts; and preventing cerebral spinal fluid leakage after transsphenoidal, posterior fossa, or spinal surgery (157).

Intraoperative Blood Salvage

In neurosurgical cases, it is uncommon to use intraoperative blood salvage, most likely because of the relatively small volumes of blood loss. Obvious exceptions to this rule are both the multilevel and revision spinal fusion surgery. The largest neurosurgical series reported dates back to 1925 when Loyal Davis and Harvey Cushing used intraoperative blood salvage techniques on 23 cases (8). The reason for its lack of popularity is unclear. However, intraoperative blood salvage can be useful, particularly in the surgical management of vascular cerebral lesions such as arteriovenous malformation (9,10). Additionally, situations that may justify the use of intraoperative blood salvage include the Jehovah's Witness patient. These patients will not accept blood transfusions but may accept intraoperative blood salvage. Relative contraindications include infection and malignancy, which could be spread to other organ systems.

Transfusions

There is no clear data or guidelines stating when a patient should be transfused. Some advocate for transfusions to keep hemoglobin 10 or greater in cases with impaired autoregulation as oxygen delivery must be optimized through increasing arterial oxygen content as adequate CBF is not guaranteed. Aside from this indication, blood transfusion has been used for vasospasm as a means of volume expansion and will be discussed later in this chapter.

PREOPERATIVE LABORATORY TESTING

The preoperative laboratory evaluation for the neurosurgical patient generally does not differ drastically from that of other surgical specialties. Laboratory analysis generally includes hemoglobin and hematocrit levels, platelet count, and because complete hemostasis is imperative, a PT and PTT is ordered. Generally accepted recommendations to begin a neurosurgery case are PT < 13.5, a platelet count $> 50{,}000$, and an INR < 1.4 (158). In addition, some neurosurgeons request a bleeding time to assess platelet function, particularly for vascular cases, although no data exist that bleeding time can independently predict operating room hemorrhage (159). If a bleeding disorder exists or is suspected a hematological consultation is warranted for correction of the coagulopathic state before surgery. Additional tests to consider are: a) the 1:1 mixing time, and b) Thromboelastography (TEG). The 1:1 mixing time is used to distinguish between the presence of either an inhibitor or a coagulation factor deficiency in a patient with prolonged PTT. A full discussion regarding the methodology and interpretation of TEG is not in the scope of this chapter. Simply understand that TEG is used as a gauge of the entire process of coagulation and can give some information regarding clotting strength. As described earlier, coagulation is a complicated process. Most laboratory tests only measure certain aspects of the whole process, but usually that is sufficient. When more information is necessary the TEG can be preformed. It gives both quantitative information about the kinetics of forming a clot, but it also gives qualitative information about the strength of that clot.

SPECIAL CONSIDERATIONS AND AVOIDANCE OF UNIQUE COMPLICATIONS

Pediatric Neurosurgery

In the pediatric population, because of relatively small blood volumes, excessive blood loss can be devastating. In children, the brain may demand as much as 50% of total body energy consumption thus underscoring further the importance of maintaining adequate oxygen and glucose delivery during adverse conditions (160). Transfusion can occur and is associated with acute and delayed complications. Acute complications include hypocalcemia, hyperkalemia,and coagulation abnormalities (161). These complications, which are prevalent in patients who have lost more than half their blood volume, can be managed with therapies to replace lost electrolytes, thromboplastin, prothrombin, and the use of fresh frozen plasma (162). Communication between the surgeon

and anesthesiologist is important both preoperatively and intraoperatively. If a particularly bloody lesion is encountered, coagulopathic states can be avoided provided the anesthesiologist is prepared to handle excessive bleeding with blood, fresh frozen plasma, and platelets on hand. Additionally, if the surgeon has difficulty controlling bleeding, a warning to the anesthesiologist or packing the wound and allowing the anesthesiologist to "catch up" will often avoid situations where the patient's blood volume and clotting factors become excessively low (163,164).

Craniosynostosis Surgery in Children

The use of blood transfusion therapy is especially high in craniosynostosis surgery where a large portion of the scalp is peeled away from the skull, resulting in bone and scalp bleeding. Intraoperative blood loss has been estimated between 71% and 126% of estimated blood volume, with total fluid replacement ranging from 94% to 180% of the patient's estimated blood volume (165). Others have reported blood loss as being dependent on the suture operated upon. Kearney et al. (166) found that blood loss ranged from 24.1% of estimated blood volume for sagittal synostosis cases to 64.7% of estimated blood volume for bicoronal synostosis cases. In a multicenter study of craniosynostosis cases involving 793 cases, 5% of patients had more than one time their total estimated blood loss (167). Although attempts were made to limit blood loss during these operations, excessive blood loss has led some to condemn these operations as too risky. To dispel some of these concerns, Eaten et al. (168) conducted a retrospective analysis of surgery for craniosynostosis in young children in 73 consecutive cases to determine transfusion requirements, to document morbidity, and to identify variables associated with blood transfusion. They determined that the suture(s) being operated on is not the most important variable in determining blood loss, but that the neurosurgeon and more likely the anesthesiologist is the more causal variable in determining if the patient is to receive a blood transfusion. They reported that none of their patients experienced any transfusion-associated morbidity.

Transfusion in Brain-Dead Patients for Organ Donation

Maintaining hemodynamic stability is critical in the brain-dead patient if viable organs are to be harvested for transplantation. Although blood transfusions may be necessary, the administration of vasopressin and, minimal dosage of epinephrine without transfusion, have been successful in prolonging hemodynamic stability (169). In the study by Yoshioka et al. (169), six brain-dead patients with severe head injury received arginine vasopressin at a constant rate of one or two units per hour (285 ± 45 units/kg/min) plus epinephrine to maintain systolic blood pressure above 90 mm Hg. This resulted in prolonging hemodynamic stability for a mean of 23.1 ± 19.1 days. Arginine vasopressin seemed to maintain a pressor response to epinephrine and vasomotor tone. These patients did not receive blood transfusions but rather lactated Ringer's solution to keep adequate venous pressure. Limiting blood transfusion reduces the risk of infectious transmission, such as hepatitis or human immunodeficiency virus, to donating organs.

Transfusion in Hypothermia

Hypothermia decreases the metabolic rate of the CNS and therefore has been investigated to reduce or prevent CNS damage after ischemic injury (170–172). Unfortunately, lower body temperatures can lead to coagulopathy and tissue damage. To avoid these complications and to sustain lower levels of hypothermia, Bailes et al. (173) investigated the use of blood substitution. Using a canine model, they lowered body temperature to near freezing point. In their pilot study, they were able to achieve complete exsanguination, blood replacement, and ultraprofound body temperatures using a continuous circulation of a blood substitute made of an aqueous, pH-adjusted, high-potassium solution containing electrolytes, plasma expander, and oxidizable substrate buffer. Continuous circulation and a core body temperature of 1.7°C were maintained for 2.5 to 3 hours. Of the eight animals, six survived the experiment, and five survived over a long period. None of the surviving dogs showed evidence of gross or microscopic ischemic injury to any CNS tissue.

Jehovah's Witness Neurosurgical Patient

To prevent the use of blood transfusions in Jehovah's Witness patients, whose religious beliefs deny use of blood products, erythropoietin therapy has been given to increase the hematocrit concentration before and after undergoing neurosurgical procedures (174). Erythropoietin therapy has improved blood counts in Jehovah's Witness patients undergoing cerebral hemispherectomy for epilepsy, (175) skull base tumor resection, (176) and spinal surgery (177). The typical dosage ranges from 100 to 300 units per kg given two to three times a week along with oral iron treatments (176). Additional techniques used to reduce blood loss in the Jehovah's Witness neurosurgical patient include preoperative embolization and staged procedures.

Optic Neuropathy

Ischemic optic neuropathy can result from intraoperative anemia and hypotension after uncomplicated lumbar

spine surgery (178–180). Risk factors that may increase the incidence of ischemic optic neuropathy include hypertension, diabetes, smoking, and coronary artery disease. After an uneventful laminectomy with moderate blood losses, the patient typically reports decreased visual acuity. In a report by Lee (178) of such a complication, the preoperative and postoperative hematocrit fell from 15.6 to 11.4 g per dL, respectively. The patient awoke and reported poor vision and a central *dark spot* in his right eye. Although in this case vision could not be returned to baseline, early recognition by the surgeon of visual loss and prompt ophthalmologic consultation may be critical in preventing complete irreversible loss of vision. Partial return of vision has been reported with early, rapid, and aggressive blood transfusion to increase the patient's hematocrit and blood pressure (181).

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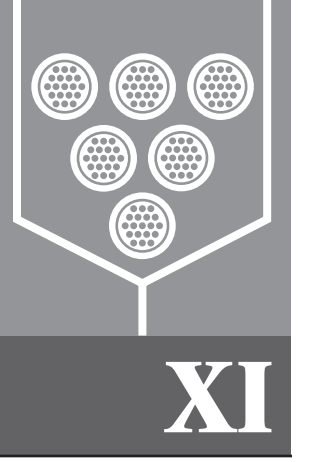
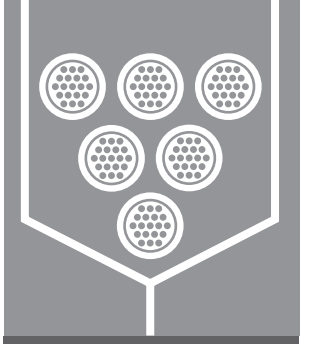


Postoperative Transfusion Issues



Transfusion and Outcome

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Transfusion has been utilized in modern medicine for over 100 years. It has been pursued with the bias that transfusing an anemic patient will improve outcome. Unfortunately this has never been fully investigated or proven. Prospective randomized trials are the only reliable ways of proving cause and effect. Such trials are the mainstay of pharmaceutical research, wherein drug companies are charged with proving not only that a compound is safe, but it is effective. Although transfusion is regulated by the United States Food and Drug Administration (FDA), the FDA has never undertaken to be prospectively test safety or efficacy of allogeneic blood transfusion. A great deal of this book has investigated the side effects or risks of blood transfusion; one could hardly call it safe. The FDA, although watching such research, has never set a goal or limitation for bloods safety. Most of the risk research over the last 20 years has focused upon virus transmission. However, today, the risks of transmission of Human Immunodeficiency Virus (HIV–AIDS) and hepatitis C are vanishingly small (1–3). Estimates and recent publications say that the risks of transmission of these viruses are in the range of 1 per 200,000,000 units transfused (3). Therefore transmission of viruses will not be dealt with in this chapter on outcomes.

Outcomes, at least for surgical physicians, are often defined in terms of success of the surgery being performed, survival, and some major complications. Adverse outcomes are those events that are not expected and the surgical/anesthesiology literature often includes the following: death, myocardial infarction (MI), stroke, pneumonia, renal failure, adult respiratory distress syndrome (ARDS), sepsis, infections (wounds, urinary track etc.), multisystem organ failure (MSOF), hepatic failure, prolonged intensive care unit stay, or prolonged hospital stay (length of stay-LOS). Few prospective randomized trials of transfusion have been conducted looking at these types of outcomes and asking the critical question: are a group of patients better or worse because they received more or less transfusions. Transfusion was part of the medical armamentarium prior to the FDA being charged with regulating blood banking. Therefore there has never been a push to go back and conduct the rigorous trials found for a new drug submission. In short, our usage of transfusions has always been predicated upon the biased and untested opinion that transfusions improve outcome. That may not necessarily be true.

PROSPECTIVE RANDOMIZED TRIALS

Prospective randomized trials are scarce in the transfusion literature. What would be most desirable to see would be hundreds of trials done over a long number of years with many different types of patients and investigated procedures. For example, it would be valuable to know if transfusion of banked blood affected outcome in coronary artery bypass surgery or in stroke victims. But neither of these has been investigated in a large enough way that prospective data is available. Transfusion is also not a medical therapy that can be given in a blinded fashion. For good pharmaceutical research to be conducted the best way is to have prospective double-blind randomized trials. There is virtually no way to blind investigators to the use of a transfusion. Certainly most conscious patients know whether they have been transfused or not. Therefore it is difficult to blind the recipients; and the bias, blood saves lives or blood is good, must affect a great deal of patient's subjective feelings of potential wellness. So, even the few

trials that do exist today are probably not blinded, although the outcome data may in some ways be partially blinded by having say cardiologists read electrocardiograms without knowing who was or was not transfused. There are but the paltry number of patients for most of these trials. The fact that more prospective randomized trials alone do not exist bespeaks the bias that exists today in medicine with regards to transfusion of banked blood. Most of these trials are simply not large enough to warrant discussing. Are we really this convinced that banked blood improves outcome?

The single largest prospective trial of transfusion was performed in the last five years (4). It was a cooperative effort between 11 Canadian institutions and sponsored by the Canadian government. Over 800 (n = 838) medical intensive care unit (ICU) patients were randomized to be transfused at a liberal (10 g per dl) or restrictive (7 g per dl) transfusion trigger. The 10 g per dl level was chosen as the historical standard from the 1980s and the 7 g per dl standard is what was recommended from the United States National Institutes of Health (NIH) consensus conference on red cell transfusions in 1987. The patients included often were: intubated, ventilated, had coronary artery disease, had respiratory insufficiency, gastrointestinal bleeds, and a wide range of other diagnoses. Over 300 of the patients had known severe coronary artery disease, but this prospective study was not focused upon patients with evolving MIs. Certainly some of the patients had a diagnosis of rule out MI as they entered the ICU but this study was not focused upon coronary artery disease alone and the safety/efficacy of transfusion. The study was randomized but not blinded. In many academic centers in the United States today it would be difficult, if not impossible, to conduct such a study. Many physicians would feel it is unethical to allow a critically ill patient to get anemic to the point of 7 g per dl.

The mean lowest Hgb levels were dramatically different between the two groups. That means that the protocol was actually followed quite closely. Overall mortality was not statistically significantly different between those transfused more liberally and those transfused less. However there was a trend in the overall group towards a lower mortality in the restrictive group and one could say it was significant at the $p = 0.1$ level. Death occurring in the hospital was however significantly different as was mortality in a low APACHE scored group and in a subgroup of relatively young patients (<age 55 years old). Both of these groups had lower mortality in the patients given less blood transfusions. Interestingly in the group of patients with known cardiac disease there was no difference in overall mortality (5). One might well have expected that transfusion should well have helped this group of patients survive, but it did not. Examining the data even closer some interesting differences in outcomes do show up. In the restrictive transfusion group, overall, the incidence of MIs was dramatically less (0.7 % versus 2.9%). The incidence of ARDS was reduced in the restrictive transfusion group (7.7% versus 11.4%), and the numbers of patients going into pulmonary edema was less in the restrictive grouping as well (5.3% versus 10.7%). Angina incidence was no different between groups and overall infection rates were not different between groups. The fact that overall infection rates were not different between groups might be to some readers surprising. Transfusion has been widely implicated as an immunosuppressive agent. There is considerable literature suggesting that patients transfused do indeed have more perioperative infections, and that will be discussed later in this chapter. However, the study by Hébert, et al. (5) was different in that many of the patients entered the medical ICU for infectious reasons. Therefore the population that his group studied may be quite different than a routine surgical population that is not infected prior to transfusion. Such a data contrast simply points out the need for more and highly specific randomized controlled trials to further understand the implications of transfusion and outcome in different patient groupings. It should be noted that these transfusions were, as all Canadian blood supplies, leukoreduced. There is no way to know if the data on any of the outcomes including ARDS, MI, and mortalities would have been any different had not the blood been leukoreduced.

Hébert, et al. (5) carried out a sub-study on 375 patients within the main TRICC study that had known heart disease. Two hundred fifty-seven of these patients were deemed to have severe coronary artery disease. There was no overall difference in mortality or MI rate in the groups given blood more or less liberally. There was however a higher incidence of MSOF in the group given blood more liberally. Once again, these data are exactly the opposite of what would be expected if banked blood was performing well, as most in medicine, have thought it would or should. Banked blood is transfused to increase oxygen-carrying capacity, and to therefore, prevent ischemic organ injury. There is no data from the studies by Hébert, et al. (5) that demonstrates that banked blood transfusion does either improve outcome to any subgroup of patients or that it increases oxygen-carrying capacity, thereby improving outcome. Indeed the data would suggest exactly the opposite.

The next largest prospective studies of transfusion were carried out in the 1990s and examined patients undergoing coronary artery bypass graft (CABG) surgery (6,7). In this study, again patients were randomized to receive banked blood at one of two different trigger hemoglobins. The differences in hemoglobin triggers here were not as large as those seen in the study by Hébert, et al. (5). Patients were

transfused either at 8 g per dl or at 9 g per dl. All outcome measures showed no significant differences between restrictive and more liberal (albeit not largely different) hemoglobin triggers. The conclusion from this study was that relative anemia is therefore quite safe. Practice has moved on considerably since this study and today levels of anemia far below those investigated in this study are routinely tolerated.

A larger recent prospective study of CABG surgery patients was carried out (8). It was not designed to compare two hemoglobin triggers, but it did compare the outcomes of patients who were transfused leukoreduced versus nonleukoreduced blood. Remember that the study by Hébert, et al. (5) used all leukoreduced blood, the only product available in Canada at the time. The study examining leukoreduced versus nonleukoreduced was prospective and randomized, but again not blinded. Mortality was not different between those receiving leukoreduced and nonleukoreduced blood. The authors did herald the fact that leukoreduced blood transfusion demonstrated a slightly but statistically shortened length of stay in the hospital (9.5 days versus 10.1 days). They neglected to point out however that the patients who were not transfused had a 6.4 day length of stay. Clearly this study was not focused on comparing in a prospective way nontransfusion to transfusion. As well, those patients who were not transfused, bled less, were less complicated, and had a wide range of fewer risk factors than those who did require transfusion. Therefore this is not a randomized trial that can be pointed to, and concluded from, that no transfusion is better than either leukoreduced or nonleukoreduced blood. However, it does point out some fallacies in our thinking. If after 1,100 patients the difference in length of stay between leukoreduced and nonleukoreduced blood is at best .5 days then we truly should not pin our hopes on leukoreduction improving outcome. Especially when those patients not transfused stay in hospital only roughly half as long. Perhaps more efforts should be focused on finding out how we can avoid transfusion rather than focusing on giving leukoreduced blood.

An even larger prospective randomized trial of leukoreduction versus nonleukoreduced blood was carried out in a general, but sophisticated academic teaching hospital (9). Any patient requiring transfusion, but not specifically indicating a medical need for leukoreduced blood was randomized to receive either white cell reduced or routine allogeneic blood. Some 2,780 patients were randomized and followed for a wide range of medical indications. This study is most notable both for its size but also for its negative outcome. There were no significant differences in: (a) in-hospital mortality (8.5% control, 9.0% WBC reduced); (b) hospital length of stay (median number of days 6.4 for control and 6.3 for WBC reduced blood); and (c) total hospital costs (median $19,500 control and $19,200 for WBC reduced). Secondary outcomes were also not different and they included ICU length of stay, postoperative length of stay, antibiotic usage, and readmission rate. Interestingly there was a significant reduction in patients who had febrile reactions to blood transfusions, $p = 0.06$. Is that decrease in febrile reaction rate alone reason enough to change to leukoreduced blood?

The prospective randomized trials of blood transfusion have been analyzed in meta-analysis form (10,11). Meta-analysis is a difficult process and one that does not always prove a scientific conclusion. The two meta-analyses that have been published have either shown that transfusion slightly worsens outcome or has no improvement upon outcome at all. Perhaps the best message from all the prospective data, what little of it there is, is that no compelling data exists to suggest that patients do better after transfusion and they may actually do quite a bit worse. The message that patients do worse after transfusion has not been well heard in anesthesia and surgery.

Hematocrit and Outcome

Our discussion will now leave the more satisfying world of prospective randomized trials and move into the rather large and confusing literature of databased analyses. Unfortunately, when one starts to look at databases a lot of confusing confounding variables can creep into the data. Only the most skilled researcher and reader can be expected to pick his or her way through this literature and garner appropriate conclusions. If databases are analyzed, they are most often analyzed in part. In other words, the research group often eliminates groups of patients and analyzes only certain subgroups from the database. This may either be appropriate or inappropriate depending on the reasons for eliminating subgroups and how potential confounders are dealt with in the analysis. Already some of the readers are lost and wishing they had not gone this far in the chapter. It is confusing.

The hematocrit and outcome literature is one of the most confusing and misleading. Hematocrit (Hct) can be both a trigger for transfusion (along with hemoglobin level), as well as a marker for disease or wellness. Patients who are anemic coming into any given operation may well be more ill, have more chronic disease, be less well nourished, have recently or chronically bled, have cancer, be receiving medications causing gastrointestinal bleeds or depressing bone marrow function, and a whole long list of other medical reasons why they are as a group more ill. Therefore, patients with a lower Hct as compared to a baseline population are by definition more ill. If any surgical

procedure is investigated, it is almost universally true that patients with a lower Hct will have a worse outcome.

Three studies regarding Hct and CABG patients have been reported and are often quoted (12–14). These studies are often also misrepresented as reason to transfuse patients. Fang, et al. (12) studied the lowest Hct level during bypass. That level is driven by a number of clinical forces including the patient's height, weight, preoperative red cell mass, circulating volume, and volume of perfusate in the bypass machine. That lowest Hct may also be a trigger point for transfusion for an anesthesia and surgery team. Patients more ill, or perceived to have a higher risk for complications, may well be transfused at a higher Hct than those at lower risk.

Fang, et al. (12) looked for a break point in their data. That break point was where the mortality was statistically different based on the lowest Hct level of bypass. It was not until patients went under 15% Hct that they could show any difference in overall mortality. Only at that Hct did mortality roughly double. Of interesting physiologic note, that level of Hct is approximately where critical oxygen delivery is determined by Hct alone. At 2.5 to 3.5 g per dl of hemoglobin animals and humans will shift their metabolism from aerobic to anaerobic or supply independent to supply dependent.

Hardy et al. (13) looked at lowest postoperative hemoglobin/Hct and found from another database of CABG patients that low Hct patients do poorly. This study looked at a relatively large number of patients from one institution. Those patients who had hemoglobin levels between 6 g to 7 g per dl or below in the ICU had a higher mortality than those with higher hemoglobin levels. Selection for low hemoglobin or low Hct might well be a marker for ischemia. But it is just as likely that it is a marker or covariate for who is transfused. It may also be a marker for overall instability or bleeding.

Defoe, et al. (14) looked at a large database from the Northern New England Cardiovascular Disease group. This consortium of hospitals pools their data for a number of different cardiac interventions. At the time that the Hct paper was published, a database of over 7,000 CABG patients existed. The database had extensive data including lowest Hct during the bypass run. What this group of investigators found was that if Hct during bypass was below 24%, the risk for perioperative mortality increased. It rose even further if the Hct was below 19%. It was certainly more than double the risk if the Hct was allowed to go below 19% during bypass. This one single study was embraced by cardiac surgery as a reason why transfusion must be given early and that the Hct during bypass must be kept at a relatively more robust level, well above 21%. Unfortunately this study, like the other two, did not take into account any data on transfusion. Therefore low Hct alone may simply be a surrogate marker for who gets transfused more often. Without examining both questions together, then the question of whether transfusion makes outcome better, unaffected or makes it worse cannot be answered. To take Hct papers out of context and liberalize transfusion behavior because of them may actually be clinically dangerous.

A large databased study of heart surgery did examine a different Hct (15). This study looked at ICU entry Hct and originally it hypothesized that ICU entry Hct would have no relationship to outcome. ICU entry Hct is quite different than lowest Hct on bypass, or for that matter, any of the other investigated and published Hcts ICU entry Hct represents the sum total of all the events in the operating rooms. It is therefore representative of whether a patient is anemic, of small body size, how much fluids he/or she received intraoperatively and what the transfusion trigger was in that operation. In contrast to the other Hct papers, this large study found that those patients with the lowest ICU entry Hct had the best outcomes in terms of MIs, heart failure, and in some subgroups, mortality. This study at least tried to take into account the affects of transfusion and it had expansive multivariate statistics to take into account almost 30 potential confounding variables. Just like the other studies however, it was not particularly focused upon the question of transfusion and outcome alone. Of interest, out of this study and others done from the same database, it was found that transfusion decisions for heart surgery are not driven by physiology and oxygen uptake requirements (16). The decision to transfuse and the Hct that triggers a transfusion is an arbitrary decision driven by the institution or rather the most influential physician in the team at any one given institution. Multiple other studies have examined the drive to transfuse for heart surgery (17,18). Low circulating red cell volume (anemia and or small body size) drive a great deal of the transfusion utilization, but so also does institutional variance. Behavior with regards to transfusion is highly variable and quite arbitrary.

More recently a large databased study (1,404 patients) has partially bridged the gap between lowest Hct on bypass and adverse outcomes (19). Renal physiology would be expected to suffer from a low oxygen delivery. In one database it was found that there is a progressive postoperative worsening of creatinine with lower and lower Hct on bypass. That would fit with the data found by Defoe et al. (14) with regards to overall mortality. However, these investigators looking into renal physiology asked the question whether transfusion improved that finding. By giving several units or more of blood transfusion, in response to low Hct on bypass the same slope towards worsening creatinine was maintained. The slope was maintained but the

overall real creatinine levels were made considerably worse. That means that transfusion did not improve outcome in response to low Hct Transfusion was additive and made renal failure far worse. Multivariate analysis to control for confounders left the data being significant and both Hct and transfusion had significant relationships to renal failure.

Transfusion and Outcome Databased Studies

Still within the realm of CABG surgery, one study stands out as unique and in this author's opinion a sentinel paper (20). A single group of surgeons looked at over 1,900 of their patients whom they followed for at least 5 years from the time of their surgery. They employed both univariate and multivariate statistics, sorting out the effects of many potential confounders. These authors employed propensity analysis. Propensity analysis is perhaps the best and most rigorous way to statistically control for confounders such as differences in patient risk entering a specific operation.

Propensity analysis utilizes the multivariate analysis to decide which if any of the confounding variables has a statistical relationship to the outcome. The ones that are statistically significant are assigned odds ratios and those odds ratios are used to then in turn score each individual patient. Patients once rescored are then paired or grouped compared to similar risk scored groups of patients with, and without, the independent variable (transfusion). It is then through comparing outcomes of like risk groups of patients that one can say whether the independent variable (transfusion) influences outcome (mortality).

Engoren et al. (20) looked at survival statistics for their patients after CABG surgery. What they found was that those patients who were transfused more had worse Kaplan-Meier survival curves than those not transfused. These data did stand up to both multivariate analysis and propensity analysis. When all the fancy statistics were done, it was found that the mortality rate for patients transfused was twice as high as for those not transfused during surgery. This was true not only early on but on out for up to 60 months (5 years).

How could that be? Transfusion is known to carry a wide range of inflammatory cytokines, active white cells and overall proinflammatory mediators (21–26). It is well known that the period of ischemia and reperfusion is a time wherein the endothelial cells are particularly at risk for further damage (27). Cardiologists have known for some time that changes in inflammation during a critical period of time, (i.e., angioplasty) can affect long-term outcome. The use of antiplatelet agents, as well as a number of newly developed anti-inflammatory impregnated stents, have improved short-term thrombosis and long-term atherosclerosis events. Prospective randomized trials have not been done with transfusion to determine if this hypothesis explains the findings by Engoren, et al. (20), but it does fit the biology. One study has been performed wherein interleukin levels were monitored in CABG surgery patients immediately before and after transfusions in the operating room (25). The fact should be remembered that a great deal of research has been done over 20 years examining the effects of the bypass machine upon inflammation. With that as a background, the transfusion of even a single unit of banked blood resulted in a systemic 15-fold increase in interleukins (25). It is quite possible that the infusion of these inflammatory mediators do indeed affect the at-risk endothelial cells and increase the risks of eventual accelerated atherosclerosis. Further work needs to be done to investigate this connection.

Vamvakas, et al. (28–32) has published a number of databased papers investigating the relationship between allogeneic transfusions and perioperative pneumonia or other infections. A consecutive group of 518 patients for CABG surgery at Massachusetts General Hospital in a database were examined for the affects of transfusion upon outcome (30,31). A number of exclusion criteria whittled the group down to 421 patients so that only those who had primary CABG without other high risk events focused the project on as homogeneous a group as possible. Two hundred sixty eight patients (64.6%) received one or more red blood cell transfusion during their surgery or immediately postoperatively. Of interest, some 17 patients received either white cell reduced or autologous red cells. This was early in the usage of white cell reduced products. The mean number of units transfused was 2.7 units. The mean length of stay (LOS) in the hospital was 8.0 ($\pm$ 0.3) days with the median being 6 days. For those patients not receiving any blood product their length of stay was a mean of 6.1 ($\pm$ 0.2) days, whereas if a patient did receive red cells, the mean length of stay was 9.1 ($\pm$ 0.4) days ($p < 0.0001$). Length of stay in the ICU was also affected by the amount of blood transfused. Those patients who received one or more units of red cells in the operating rooms had a mean LOS of 58.2 ($\pm$ 4.8) hours as compared to 35.1 ($\pm$ 7.5) hours ($p < 0.0001$). The number of units transfused could account for 38.7% of the variation in postoperative LOS ($p < 0.0001$). Only prior myocardial infarction, diabetes mellitus, chronic respiratory insufficiency, and emergency surgery had any more strong correlation with length of stay. In a multivariate analysis loading in some 20 potential confounders or known predictors of length of stay when RBC transfusion was loaded into the models the LOS increased 0.837% per unit of red cells transfused. They did conclude that the amount of blood transfused was the leading predictor of length of stay in the

hospital (30,31). Their model of multivariate analysis could not however distinguish that it was cause and effect or that it was possible to attribute all of the relationship to blood transfusion. After their exhaustive statistical analysis they concluded that confounding variables were still strongly related and that blood transfusion was not necessarily clinically relevant in causing the increased LOS seen as a statistical relationship.

This stands in contrast to what the same author had concluded only 1 year prior in the same journal, *Transfusion* (30). In that earlier publication looking at the exact same database from the same institution with the same patients Vamvakas had a much stronger message. This earlier paper had focused upon postoperative pneumonia and the length of storage of transfused red cells. There was a strong association between the administration of red cell transfusions and perioperative pneumonia. Fifty-three patients were transfused and developed either pneumonia or a wound infection. There was a strong relationship between the age of the blood transfused and the occurrence of either pneumonia and or wound infection. To quote this paper; (31) "In an analysis of all patients, the risk of pneumonia increased 5% per unit of non-WBC-reduced allogeneic RBCs and/or platelets received ($p = 0.0584$). Among 269 patients given RBCs, the risk of pneumonia increased by 1% per day of increase in the mean storage time of the transfused RBCs ($p < 0.005$)" (31 p. 708).

Perioperative infection has been reported to be increased in a large number of databased retrospective reviews of transfusion (8,27–31,33–35). Such relationships have already been discussed elsewhere in this book and in an entire chapter relating transfusion to immunosuppresion. A quick look at a meta-analysis of papers on transfusion and infection shows that almost all papers show an increased risk of infection (36). In the 1970s and 1980s when renal transplantation was just getting going it was the practice to transfuse every renal transplant patient with red cells and or plasma. A number of papers noted that acute rejection and later more chronic rejection was decreased if patients were transfused at the time of transplantation. Today, some have said that a unit of non-WBC reduced red cells has the immunosuppressive effects of a single dose of cyclosporine. If the renal transplantation literature is to be believed, allogeneic blood transfusion may well have effects far beyond that single dose of cyclosporine (37).

In general surgery, a large database looked at transfusion, infection, and mortality (38). Over 6,000 patient's records undergoing noncardiac, nonorthopedic, general surgery at a Veterans Administration Hospital between 1995 and 2000 were retrospectively examined. There was a well tolerated and expected drop in Hct during and after surgery. The mean Hct dropped from 38% to 29.5%. That meant that the majority of patients (84%) were anemic (<36% Hct) after surgery. However postoperative anemia was well tolerated. This study looked not only at the affect of any transfusion, but was able to break down the risks to only one unit or greater than four units transfused. If a patient was anemic to begin with prior to surgery, he or she was at least five times as likely to receive a transfusion during and immediately after surgery. That is not surprising. But if a patient received even one unit of blood there was a statistically detectable increase in both infection and mortality (odds ratios of 1.06 and 1.08 respectively). These odds ratios are not large, but they were statistically significant at $p < 0.0001$ and $p < 0.001$, respectively. If the patients received four units or more then the risks of infection and mortality dramatically climbed. The odds ratio for infection went up to 9.28 (95% confidence interval 5.74 to 15.0) and the odds ratio for increased mortality went to 2.84 (95% confidence ratio 2.07 to 3.89). Multiple logistic regression found that blood transfusion did still stay as an independent risk for infection and mortality when other confounders were loaded into the models. The conclusion of this retrospective study was that it is important to treat preoperative anemia and to practice methods to preserve native red cell scavenging.

In orthopedic surgery there have been a number of studies examining the effects of transfusion either allogeneic or autologous red cells (39–41). The literature here is not without some controversy. However, a significant number of studies do note that patients given their own blood preferentially at the time of surgery have less infection than those given allogeneic blood. The odds ratios reported in prospective randomized series have been between 1.5 fold to 3.5 fold increased risk of infection with allogeneic blood. Computer models of the cost of autologous blood in the early to mid-1990s focused upon the cost of saving a life by switching to autologous blood (42). These computer models took into account the major transfusion risks of lay focus, hepatitis, and AIDS. When such computer models were constructed and because the blood banking industry was making such strides to control the spread of these viruses it was found that it would cost approximately one million dollars to save a life by employing autologous blood. However, these computer modeling studies ignored all other risks of blood transfusion and summarily dismissed the risks of either bacterial contamination or of immunosuppression as either unsubstantiated by the literature or unable to be quantified. Therefore they did not take these, now more well understood, risks into account and compute costs to them. In a subsequent model published in the same journal as the prior work it was shown that the effect of immunosuppresion leading to increased perioperative infection makes the use of autologous blood

extremely cost effective (34). The cost of saving a human life by employing autologous blood when infection is taken into account is more in the several thousands of dollars not in the millions of dollars.

Immunosuppresion by blood transfusion is thought to be caused by a number of mechanisms and again this is discussed elsewhere in the text. However, some of the immune down regulation is thought to be due to donor white cells infecting or living in the recipient. These white cells decrease the effectiveness or compete with the recipient's helper T cells leading to immune modulation. The push therefore has been to move to WBC-reduced or filtered blood. That was first proposed in Britain as a way to decrease the spread of the abnormal proteins called prions that are thought to be the causative agents of mad cow disease or variant Creutzfeld-Jacob Disease (vCJD).

Leukoreduction is costly, adding at least 35 to 50 U.S. dollars cost to each unit harvested. Britain, Western Europe, and Canada adopted leukoreduction as standard for their blood banking industry without large prospective randomized trials. The United States FDA has said it may be advisable but to date has not mandated such a practice. Just in the last 5 years retrospective and some prospective studies are emerging examining the outcomes in patients with and without leukoreduction (9,43–51). Several prospective randomized studies are also coming to the literature and to summarize this it is unclear just how effective leukoreduction is in decreasing the immunomodulation effects of transfusion. In a prospective randomized trial conducted in CABG patients, length of stay was focused upon as the main outcome variable (8). Length of stay in patients' transfused nonleukoreduced blood was 10.1 days whereas LOS in patients receiving leukoreduced blood was 9.5 days. That was statistically significant and the authors made the title of their paper based upon that observation. However, it should be pointed out that 0.6 days may neither be clinically significant nor impressive. The length of stay for patients not transfused was highly significantly different at 6 days and that does stand out both as clinically and statistically significant. Clearly those patients not transfused were a more robust and healthier group who were less anemic than those not transfused so this study is not a perfect study to truly understand the independent risks of transfusion. But this study does illustrate perhaps the rather small gains that can be made by switching to leukoreduced blood.

A retrospective review of over 2,000 patients in Britain undergoing either CABG surgery or major orthopedic surgery before and after the institution of leukoreduction showed no difference at all in perioperative infection rates (48). Other retrospective studies have either shown no difference or some small differences in infection rates.

The latest data has examined now a comparison between autologous blood and leukoreduced blood in a prospective trial for knee replacement or unilateral hip replacement (9). Although a good-sized study by transfusion standards, 308 patients, it was not huge. One hundred one patients received no transfusion, 85 received preoperative autologous donation and received some of their blood back. One hundred patients received allogeneic white cell reduced blood. Twenty-two patients received a combination of autologous blood and allogeneic white cell reduced blood. The difference in infection rates was striking. Overall the infections, defined by orthopedic surgeons blinded to the type or presence of transfusion. Urinary tract infections (confirmed by culture and excluding patients with preoperative UTI), pneumonia, and wound infections (confirmed by culture and purulent drainage) were all included. Isolated fever and or white cell count elevation without any other confirmations were not included. Overall for all 308 study patients the perioperative infection rate was 6.8% and that is consistent with other surgical literature. Interestingly those patients who received no transfusion at all had an infectious rate of 6.9% whereas those who received autologous blood had an infectious rate of 1.2%. If the patients received allogeneic blood the infection rate climbed to 12.0%. The length of stay in the hospital for patients with a preoperative infection was statistically longer as well. Clearly use of leukoreduction alone does not solve all of the problems of increased perioperative infection.

The cancer literature has investigated a relationship between blood transfusion and cancer recurrence (50, 52–54). Colon cancer and prostate cancer operations are the most frequently quoted studies. Here the data is not as clear as for overall increased infection rates, but at least in a number of studies there exists an association between perioperative transfusion and increased rates of metastatic disease. In one study looking at 740 patients with a median follow-up time of 6.8 years undergoing colon resection there were quite striking differences in survival time between those patients transfused and those not transfused (4.6 years not transfused versus 3.0 years transfused, $p = 0.0004$) (53). A multivariate analysis attempting to control for possible confounders of extensiveness of disease found an odds ratio of 1.5 (95% CI, 1.1 to 2.2). The conclusion was that there was a striking independent relationship between transfusion and cancer recurrence. As stated earlier, this has not been carried out in a larger number of other cancers and in some no relationship can be found. The data from colon rectal cancer does fit with the overall picture of nonwhite cell reduced blood being immunosuppressive.

In trauma surgery the idea of blood carrying immunologic effects has been rather well embraced (55,56). MSOF

is the bane of trauma surgery existence. A patient may survive the initial injury and resuscitation only to go on to linger in the intensive care unit for days or weeks. Lungs, liver, kidneys, and other organs undergo partial or total failure and contribute to the risk of sepsis shock and death. Moore and others undertook a 55-month long cohort study of severely injured patients. They collected a great deal of data including Glasgow coma scale, injury severity score, age, sex, comorbidities, injury mechanism, systolic blood pressure on admission to the emergency room, blood gases, lactates, and amounts of blood transfused at various horizon points in their care. Five hundred thirteen consecutive patients with an injury severity scale of greater than 15 who were older than 16 years of age and survived longer than 48 hours were followed. There were strong multivariate relationships between dosage of blood transfused and the incidence of multisystem organ failure. Thirteen of 15 logistic regression models showed that blood transfusion was an independent risk factor for multisystem organ failure. Similar work by some of the same authors showed that in trauma patients who had MSOF, the age of the blood transfused was older.

In a database of 9,539 patients requiring hospital admission to a level 1 trauma center between 1997 and 1999 the effect of blood transfusion upon systemic inflammatory response syndrome (SIRS) was investigated (57). A score for the relative amount of SIRS demonstrated was given to each patient from 0 to level 4. Of interest in patients with low SIRS scores the percentage of patients who were transfused was low. As the SIRS scores raised so did the percentage of patients receiving transfusion. Mortality followed severity of the SIRS score. Multivariate analysis showed that this association was not only significant but independent of potential confounders. Some investigators have postulated that it takes at least two or more adverse events coupled together to create MSOF or SIRS. One of the groups of investigators who looked at MSOF has suggested that late transfusion after trauma sets up polymorphonuclear leukocytes to adhere via mechanisms of platelet activating factor (PAF). PAF is present in high quantities in allogeneic stored blood. It rises the longer blood is stored and signals, not only platelets to activate and adhere, but also for platelet white cell conjugates to proceed. The enhanced PMN activation seems to lead to excess oxygen-free radical production by PMNs which further leads to tissue damage. This is one mechanism investigated to date but whether it is the presence of cytokines, acid, base, more red cell ghosts, or simply dysfunctional red cells that block capillary oxygen delivery that causes these effects of SIRS and MSOF is unknown. It does appear real.

There is no data to suggest that transfusion to any given hematocrit or hemoglobin improves respiratory function. Indeed the data on inflammation, SIRS, MSOF, and now data on transfusion-related acute lung injury (TRALI) would suggest that giving allogeneic blood potentially harms lung function (58). Vamvakas, et al. noted that there was no advantage to transfusion in ability to wean patients from the ventilator. Hébert, et al. similarly noted that blood transfusions do not improve patients' ability to be weaned from a ventilator. If anything, both of these studies show that respiratory dysfunction is increased with transfusion.

Databases Regarding Transfusions and Coronary Angina/Myocardial Infarction

The question of when to transfuse for patients with known or expected coronary artery disease has been unanswered to date. The NIH consensus conference said that routine transfusion triggers should be somewhere around 7 g per dl but that in the face of significant coronary artery disease the transfusion trigger should be higher, perhaps at 9 g per dl or above (59). That was their recommendation but there was little evidence and no prospective randomized trials to support such conclusions. Hébert's work from the TRICC study has already been discussed and in one way it should be interpreted to say that there is no support for transfusing these patient's at a higher Hct (4,5). There was no survival advantage for patients given blood more liberally than those in whom it was restricted. However those patients with known coronary artery disease transfused more liberally had a higher incidence of MSOF (5).

Recently two large and somewhat controversial data-based studies have been published in large national journals examining the relationship between transfusion and outcome (60,61). Their conclusions are exactly opposite. So the question is still open for considerable debate and the need for a prospective randomized trial was never stronger.

Wu, et al. (61) undertook an exhaustive statistical analysis of 234,769 acute MI patients in a United State Health and Human Services database for 1 year 1994 to 1995. This Medicare database looked at patients presenting to the emergency rooms with the complaint of angina and rule out MI. It was published in the *New England Journal of Medicine* and accompanied by an editorial extolling that now at last we knew when to transfuse. It hardly does that and indeed the data analysis is so fraught with troubling eliminations and lack of equal discussion of added risk for patients who were transfused at higher Hct that one has to wonder about bias involved.

It is well worth examining this paper carefully and reading it in its entirety. The original 234,769 patient database was whittled down to a database for analysis of 78,974 patients. These were only patients 65 years of age or older. This is still a large database and a huge set of patients to analyze. But, why were each of the subgroups of patients

eliminated? That means that only one third of the overall robust group of patients were eventually utilized. All patients under age 65 for example were eliminated. If transfusion was effective in relieving angina and myocardial infarction would it not be as likely to improve outcome in patients under age 65 as over that age?

At any rate, once the groups were eliminated and the 78,974 remaining patients were left in, the Hct groups were created descending by three percentage points each. Anemia was defined as any patient with Hct less than 39%, perhaps a liberal definition of anemia. That was present in nearly 50% of all the patients. Of all the patients only 3,680 (4.7%) received a blood transfusion even though by the authors own definition almost 50% were anemic. Patients who had Hct equal to or less than 30% accounted for only 4.2% of patients (n = 3324). The authors noted that patients who had Hct of less than 33% on entrance into the emergency department and received one or more units of transfusion had a better survival than those patients who were not transfused. Kaplan-Meier survival curves were constructed at each Hct and for patients that did or did not receive a transfusion.

The finding of improved survival was with univariate statistics alone. There was no multivariate analysis or propensity analysis to control for possible confounding variables. The major outcome variable here was mortality. The authors eliminated so many groups from the original 234,769, but they left a number of patient groups in the mix that might well have skewed some of the results. For example, included were patients who were designated do not resuscitate (DNR), but eliminated were patients with known terminal cancer. Clearly some patients must have a DNR for reasons other than terminal cancer since the group that had a Hct of 30% or less, the one in which transfusion was deemed effective, had a 22% DNR rate. The group with Hct 33% or greater, had a DNR rate less than one half of that. Clearly when a patient enters the emergency room and is designated a DNR patient yet has chest pain, most physicians would be less likely to transfuse such a patient. Wu, et al. (61) handled their data by stating they checked the Kaplan-Meier survival curves with and without DNR patients included or excluded and saw no overall differences. Perhaps that is not the best statistical method to handle potential confounders. When one looks at other vital factors and compares the patients who were at 30% Hct or below with those in the higher Hct ranges, many other differences show up. The low Hct group, notably only 4.7% of the patients, were a much more ill group and far less likely to receive either antifibrinolytic therapy, cardiology consultation, coronary intervention, or even emergency cardiac surgery. The article does not allow the reader to see how these potential confounders are weighted in the groups that did and did not receive transfusions therefore one cannot possibly know if the finding of increased survival with transfusion is real or a bias based on the confounders.

When the data is more closely examined, it is apparent that for patients who were relatively anemic (<39% Hct, definition by Wu, et al. (61)), but 33% Hct or greater if they received a blood transfusion, the effects were quite deleterious. In some groups the risk of death rose up to fivefold. However, the focus of the entire paper was on how wonderful it was to know that transfusion worked so well in patients with a Hct below 30%. Clearly this paper has many problems and should not be quoted as proving that transfusion for persons with coronary artery disease is effective.

Rao, et al. (60) has just recently been published and strongly contrasts with Wu, et al. (61) Wu, et al. relied on government databases both for patient entry and for survival data. His study had little information on timing, amount, or motivation for transfusion. Rao et al. (60) looked at prospectively collected data from three carefully monitored cardiology drug trials of patients undergoing angioplasty for evolving MIs. The three trials were known as: the GUSTO IIb, PURSUIT and PARAGON B trials. These trials focused upon the use of angioplasty techniques along with supplemental glycoprotein IIb/IIIa inhibitor administration after angioplasty. They were not devised to examine transfusion efficacy nor were there transfusion guidelines in any of the trials. However, because these trials were all in relationship to new FDA approval filings for pharmaceutical agents, detail upon the use of transfusion and detail regarding adverse events was diligently kept. Just as it is recommended that readers go to the source for the Wu, et al. (61) article, it is equally recommended that they review this one. It has generated perhaps as much stir as the Wu, et al. (61) article.

Rao, et al. (60) examined 24,112 patients that underwent these three trials. Roughly 10% of all these patients underwent at least one unit of banked blood transfusion. The timing of the transfusion was captured and different odds ratios for death depending upon the timing of transfusion are reported in the paper. The primary outcome variable was 30-day mortality. MI was followed as was the composite endpoint of MI/death. Patients who underwent transfusion were older and were more ill with a number of key comorbid diagnoses than those that were not transfused. The unadjusted mortality rate in those who received a blood transfusion was 8.00% versus 3.08%; $p < 0.001$. MI occurrence again with unadjusted data, not taking into account the potential confounders, was 25.16% in transfused patients versus 8.16% in those not transfused; $p < 0.001$. Death and MI together as a composite endpoint occurred in 29.24% of the transfused patients and 10.02% of the non-transfused patients; $p < 0.001$.

The authors used Cox proportional hazards modeling, a multivariate analysis method, that incorporated transfusion as a time-dependent covariate, and the propensity to receive blood and a landmark analysis. The statistical analysis was quite complicated and interestingly requires a full page of the paper just to outline how each potential confounder was handled in multiple different multivariate analyses. Overall transfusion was associated with an increased hazard (odds ratio) of death at 3.94 (95% CI, 3.26 to 4.75). To translate that into laymen's terms, patients who were transfused had almost a fourfold increased risk of death. That stood out independent of the covariates and confounders.

When Rao et al. (60) examined the effects of Hct on mortality and/or MI and the involvement of transfusion, the data gets even more interesting. There does appear to be a cutoff at around 30% Hct. For patients who were transfused with initial Hcts above that level the odds ratios for mortality were 168.64 and 291.64. Those are huge odds ratios. They are however consistent with the data that Wu, et al. (61) glossed over in that any patient with a relatively normal (>30% Hct) who is transfused and who has an evolving MI will have a high death rate. Rao, et al. (60) found that if the initiating Hct was below 30% the odds ratios showed no statistical increased risk of death with transfusion. Notably they did not show however any advantage of survival conferred by transfusing such seemingly rather anemic patients in the face of an evolving MI.

How do we as practitioners reconcile these two diametrically opposed studies? Both of them have large databases that were analyzed. The study by Rao et al. (60) does seem to have some advantages in terms of how it was conducted and the available data within the database that his group worked from. The study also seems to be much more statistically correct in the way it handled potential confounders. All that being said, it remains quite clear that what is needed is a randomized prospective trial of transfusion in coronary artery disease and especially in evolving MI. At this time no one can claim that they know for certain what Hct level to use as a trigger or whether a more liberal or restrictive transfusion trigger is better for these patients.

Platelet Transfusions and Outcome

Most surgeons and anesthesiologists when thinking about transfusions, think first and foremost about allogeneic red cell transfusions. The variability in their utilization makes it quite clear that we do not know when it is best to transfuse these products (16,17). Red cells are infused supposedly to increase oxygen-carrying capacity. Transfusion of coagulation blood products, including fresh frozen plasma, cryoprecipitate, platelet concentrates, and specialized factor concentrates, are also transfusions. There is relatively little data about these blood products and patient outcomes. There is some data from FFP showing that the products contain some cytokines and can have some level of immune modulation, but not anywhere as much as red cell products or platelet products.

Platelet products are either harvested at the time of red cell harvest through a centrifugation/separation process or by platelet phoresis. Once harvested the units are stored up to 5 days at room temperature on rockers that move the fluid around inside the plastic storage bags. The changes inside of the storage bags are profound since the same low oxygen environment is encountered here as is seen with red cells products. Platelets become activated and conjugate with WBCs. Cytokine levels have been reported to rise as high as 1,000-fold the levels seen when the blood is directly harvested. The platelets themselves express their glycoprotein ligands and therefore they are thought to be partially activated and quite pro-thrombotic. The biology of these products makes them suspicious that recipients of such infusions might well suffer adversely. However, in the perioperative surgical settings, if a patient is bleeding and thrombocytopenic, there is no other alternative but to use platelet concentrates or single donor platelet pheresis units to reestablish an appropriate circulating platelet count.

Just as Rao, et al. (60) used previous pharmaceutical databases to examine the effects of red cell transfusions, Spiess, et al. (62) went to the pharmaceutical trials data and looked at platelets. Bayer Inc., conducted five major international trials of the drug aprotinin in heart surgery before filing for an indication with the FDA. Aprotinin decreases inflammatory mediators' production during heart surgery and decreases bleeding as well as transfusion utilization. The five clinical trials and a pilot study were conducted in the early 1990s. They were prospective, randomized, and double-blinded to the administration of aprotinin. Each study had defined transfusion criteria, and most importantly the timing and type of blood products transfused was carefully recorded. Bleeding and transfusion were main outcome variables for the drugs approval by the FDA and therefore these drug trials have accurate and robust data regarding the use of transfusion in heart surgery. They also have extensive and rigorously collected data on patient outcomes.

Of the overall database some 1,700 patients were analyzed by Spiess, et al. (62) in an attempt to understand whether platelet transfusion affected patient outcome. Over 800 patients received either high dose aprotinin or had been randomized to the placebo group and did not receive the drug. Therefore in the placebo group one could study the affect of platelet transfusions alone upon outcome whereas the anti-inflammatory effects of the drug may have had an interactive effect in the high dose aprotinin group. Of the overall group 284 patients or 14.4% received one or more platelet infusions. Patients who received platelet

transfusions were more likely to be older, non-Caucasian, to have a low ejection fraction (<30%), and to have had a prior MI. Clearly they were more ill going in to the operation than patients not receiving platelet transfusions. Univariate analysis showed that patients who received platelets were more likely to have a postoperative infection, stroke, and/or death. Stepwise logistic regression analysis adjusting for significant potential confounders still found that there was an independent and statistically significant association between platelet infusion and the univariate findings of infection, stroke, and death. Propensity analysis was carried out much the same way it had been utilized by Engoren, et al. (20) to investigate long-term mortality after red cell transfusion. The propensity analysis showed that there were significant associations between platelet infusions and increased use of vasopressors, respiratory failure, stroke, and death. The odds ratios for stroke was 2.59 (95% CI, 0.99 to 6.67; $p = 0.05$) and the odds ratio for death was 4.76 (95% CI, 1.65 to 13.73; $p = 0.009$).

An accompanying editorial in the journal *Transfusion* took some exception with the findings of the article and noted that even the most stringent propensity analysis cannot account for all confounders (63). The question does remain open to some degree how much platelet transfusion causes or contributes to the death and stroke increases seen in this study. However, the findings do fit with the biology known regarding the inflammatory nature of platelet products as well as their pro-thrombotic activation.

In leukemia and bone marrow transplantation it is now well known that patients who receive more frequent and larger numbers of platelet transfusion do worse and have early deaths. That could well be due to the fact that those patients requiring more transfusions are more ill and poorer responders or in worse overall health than those patients not transfused. However, it has also become apparent that aggressive prophylactic platelet transfusion should not be carried out for these patients.

In a study of almost 6,000 patients undergoing CABG surgery across the world it was found that early establishment of platelet inhibition improved outcome (64). Those patients given aspirin in the early postoperative period did better with fewer MIs and deaths than those patients not receiving the drug. Buried in this paper was an analysis of platelet transfusions. It was noted that platelet transfusions were highly associated with an increased risk of death, almost the same amount as was found by Spiess, et al. (62).

Platelet transfusions have been utilized in heart surgery quite liberally in some centers. Up to 40% of patients in some centers are given platelet transfusions whereas in other centers no one receives a platelet transfusion. The message from the little bit of literature available today is that liberal and/or prophylactic use of platelet transfusions may be quite dangerous and contribute to an increase in stroke and death rate (62,63,65). Just as in the red cell transfusion literature the only way to fully understand cause and effect would be to do a prospective randomized trial. That, to date, has not been accomplished.

SUMMARY

A great deal of data and some of the studies examining relationships between transfusions and outcomes have been summarized in this chapter. The emphasis seems to be that transfusions increase the risk for adverse outcomes: infections, pulmonary dysfunction, stroke, MI, and death. That is counterintuitive since red cell transfusions are given to try to prevent these adverse events. Most of the data presented was from databases wherein the data was not collected to focus upon the risks of transfusion alone and also most of the data was not prospective or randomized. The only prospective and randomized data either shows that transfusion has no effect on outcome or that patients, even critically ill ICU patients, do better with less transfusion.

Blood transfusion must though do some good and it must save some lives. Clearly it does, but we need to study that all-important question with unbiased and critical science. To date, blood transfusion has been driven by beliefs and lore, not science. What is emerging from all of these databased papers is a crying need for prospective randomized trials. The construct of such trials may not be easy. Ethical questions will arise and certainly institutional and individual bias will influence and prevent some prospective trials from ever really addressing the biggest clinical questions. Unfortunately blood banking has evolved and been granted a special set of criteria by the FDA with regards to both safety and efficacy. Focus has always been upon developing means to increase supply so that demand never outstrips the supply. For a patient to die with anemia due to lack of a blood supply would be in most clinicians minds criminal. But, it appears that our use of transfusions are perhaps far too liberal, since the data so often points to our use of transfusion worsening outcome not improving it. There must be a turning point or balance point at which the risks of transfusion are equal or less than the risks of anemia. That point needs to be individualized for each patient and a great deal more science must be done before we know whether transfusion helps patients in any of a large number of perioperative groups.

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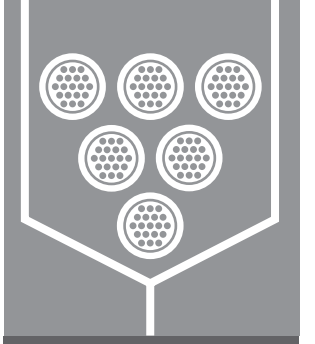

The Transfusion Decision

47

Aryeh Shander *Bruce D. Spiess*

The decision to transfuse a patient, with either a red cell product or coagulation component, should not be taken lightly. This constitutes a summary chapter, and the decision to transfuse an individual patient should involve a great deal of information from this text. Transfusion medicine is changing rapidly. The risks of viral transmission are the lowest they have ever been in the history of blood banking (1–3). Yet they are not zero and never will be (1,4–6). Allogeneic blood still carries a wide range of other potential problems and risks (7,8). Therefore, although the blood supply is the safest it has ever been, there is little reason to liberalize transfusion practices. Transfusion, like all treatments in medicine, is the culmination of a risk–benefit ratio. The treating clinician must weigh the risks and assess the benefits before proceeding. All too often in the perioperative period, the patient has been rendered unable to participate in any part of the transfusion decision (due to anesthesia and sedation). Therefore, unlike many other therapeutic decisions, the perioperative transfusion decision may be made without patient input. Without such patient input, one would expect that the transfusion decision would be made only after considerable thought and contemplation. All too often, little thought is involved in that decision.

THE RISKS

The risk–benefit ratio of transfusion has been extensively discussed in the chapters on infectious transmission and noninfectious risks of transfusion (Chapters 3, 7, 37). These risks pertain to infectious risks to all allogeneic products that have not undergone heat treatment. Therefore, all red cell products, whole blood, fresh frozen plasma (FFP), platelet units, and cryoprecipitate carry such risks. Some factor concentrates, antithrombin III, and human albumin may be virus-free because they have undergone pasteurization. Additives to allogeneic units rendering them free of viral transmission are experimental.

The risks of viral transmission appear to be changing every year and as such they are improving. Greater than 90% of posttransfusion hepatitis is due to hepatitis C virus. In the 1980s, as many as 10% of transfusion recipients were sero-converting (9,10). Today the per unit incidence of hepatitis C virus sero-conversion is 0.03% (1). Those data are the best yet reported in the literature and come from Johns Hopkins Medical Center. No other reports have since been published either confirming or bettering that statistic. It may well be that the incidence is even lower because of the introduction of other surrogate testing for liver dysfunction. However, before practitioners are tempted to liberalize our transfusion triggers, some reality should be discussed. This is a single report. Some pockets within the United States may have a higher exposure rate (and thus early viremia) than what occurs in the donor population for this major academic medical center. Also, this report represents the best data from one of the finest health care centers in the world. The remainder of the world may not be able to match such statistics. At the recent World Congress of Anesthesiologists, reports on transmission of hepatitis virus and acquired immunodeficiency syndrome (AIDS) were forthcoming from central Africa and Australia, Western Europe, and the United States. The variability was astounding, and in some of the African countries, levels of viral transmission for hepatitis and AIDS may well exceed 40%. Therefore, those reading this textbook should not be hasty to judge that all blood

sources have the same low risk for hepatitis as seen in the report from Johns Hopkins. That report alone should not trigger a liberalization of transfusion.

The risk of AIDS transmission has changed the way transfusion medicine is practiced worldwide. Its outbreak into the industrialized world has caused the lay public to pressure the medical community into enhanced testing for all viral illness in transfusion. Scandals in France have led to the imprisonment of officials from blood banks. Indeed, consumer confidence in Western Europe for transfusion products has created a crisis of scarcity of donors. This may not make rational sense, but it has occurred. Once again, the risks of viral transmission are the lowest they have ever been. Various reports over the last 5 years have set the risk of AIDS in the United States to be between 1 in 450,000 and 1 in 660,000. A most recent report puts that number at approximately 1 in 1,000,000 per unit of transfused blood (3,4,11,12). But once again, even with other enhanced screening tests such as human immunodeficiency virus type 1 (HIV-1) antigen, parts of the world where HIV is prevalent should be at much higher risk for transmission of AIDS by blood transfusion.

These two viral entities, hepatitis and AIDS, may give the clinician an impression that the risk of viral transmission is so remote that in his or her individual patient they can be ignored and transfusion can go on without so much as a thought of such transmission. Indeed, some practitioners have voiced feelings that transfusion triggers could be liberalized. Some other statistics should be examined before embracing such thinking. In the U.S., 22 million units of blood components are transfused every year (13). Probably 60% of these units are transfused in the perioperative period, with anesthesiologists and surgeons making the transfusion decision most often. The mean number of units transfused per patient is in excess of 5.4 units (14). Although that data may be somewhat dated by now, it probably holds true, or the number may be even higher as the driving force behind the ever-increasing use of blood components is the inception of extremely complex and hemorrhagic surgery such as hepatic transplantation.

With each patient receiving an excess of six donor exposures and the risk of viral transmission being 0.03%, mathematics alone would suggest that the risk per patient might be much higher. Some estimates would put the patient population at risk for new viral infection (hepatitis) to be between 20,000 and 60,000 individuals. Some 25% to 50% of those infected will develop symptoms that may complicate their hospital course and that 20% may go on to develop chronic active hepatitis, whereas some 10% will go on to fulminant liver failure, death, or require hepatic transplantation (15). The prevention of these awesome statistics starts with each individual clinician at the time of the decision to transfuse. Any movement toward liberalization of a transfusion trigger will certainly increase these numbers for patients contracting hepatitis and therefore increase the eventual hepatic failure/transplantation requirement and death rate.

The most common viral transmission occurring in allogeneic blood is that of cytomegalovirus (CMV). Most healthy patients have a subclinical flulike response or no response at all to CMV. However, in immunocompromised hosts such as those undergoing organ transplantation or those having surgery after some type of chemotherapy, CMV can be catastrophic. Once again, the exact statistics are not known, and most clinicians focus on the risks of hepatitis and HIV when thinking about transfusion risks. In the future, CMV may well become a major risk factor of allogeneic blood transfusion. Finding CMV-negative blood may not always be possible if the medical community begins to demand it for many or most transfusions. Perhaps other pathogens may enter the blood supply and may be discovered to be transmissible. Although the focus has been on viral disease transmission in the United States, in other parts of the world, parasitic diseases are extremely important, including malaria and babesiosis.

Noninfectious risks, unlike viral transmission, have not substantially changed since the increased public awareness of transfusion risks. Minor transfusion reaction including urticaria, fever, and malaise still occurs quite frequently (16). Blood units may be wasted, medications given, and even workups for transfusion reaction begun because of such reactions. No one has studied the cost of such minor reactions. Under anesthesia, during surgery, and often in the immediate postoperative period, patients are not able to express the sensory complaints associated with these reactions. Hives may be noticed by the observant anesthesiologist or surgeon, but more often than not, the patient is draped and large segments of skin are not readily available for inspection. Fever and hypotension, also nonspecific markers of transfusion reaction, are not infrequent and nonspecific events during anesthesia and surgery and may or may not create a link in the clinician's mind with transfusion. If the anesthesiologists and surgeons do make a temporal link between a blood transfusion and changes in the vital signs, often the blood transfusion will be halted. There are no data on how often this results in aborted surgery or other interventions. However, in awake nonoperated patients, the incidence of febrile or minor transfusion reaction may be as high as 10%. Nonhemolytic (1% to 5%) and the feared event of hemolytic transfusion reaction (1-6,000 to 1-33,000) can be difficult to discern in the anesthetized or heavily sedated patient (16,17). Vital signs change and hematuria may be unreliable or caused by a wide range of events unlinked to transfusion.

Immunosuppression is almost certainly a response to allogeneic transfusion (8,18–21). The data still garner some

controversy, and the extent of its impact on immediate hospital course, prevalence of other opportunistic infections, and recurrence of cancer is still debated (22,23). However, it does appear that white cell transmission in red cell products and particularly platelets may be an etiology for the resulting immunosuppression. Clearly, higher rates of other infections have occurred in matched randomized studies using either allogeneic or autologous blood. Those receiving autologous blood had lower incidence of infection (19). All data gathered to date regarding reduction in viral transmission have no impact on the incidence of immunosuppression. The use of white cell filtering of red cell products may decrease the risk of immunosuppression in the future, but that technology is still being investigated, and indications and cost-effectiveness studies have not been done in enough situations to allow the medical community to widely embrace the technology.

Practices today are changing in response to market forces relating to costs. Blood transfusion may be costly, and modification of perioperative transfusion strategies can therefore influence costs. Data on the costs of components are now available. The per unit cost of a red cell transfusion exceeds $155 to $260 (24–26). This takes into account not only the unit charge, but also risks of transfusion. We have no way of estimating the costs of personnel time for administration, vigilance of complications, and workup. With an estimated 12 million red cell units transfused in the United States per year, that means a cost of over 2 billion dollars annually. The number could be easily twice that, and the cost of other components including coagulation components may be in the range of 1 to 2 billion dollars. Those are estimates of the cost of components alone. Other added costs such as intravenous sets, saline, blood warmers, medications to treat febrile reactions, works for blood reactions, and so on are not even attempted to be analyzed. Attempts at understanding the long-term cost impact of transfusion based on the risk of hepatitis and HIV transmission have put the added cost at roughly $5 to $10 per unit (26). This may seem small, but it is based solely on the latest and best statistics from the Johns Hopkins report. It is also based on a number of assumptions and may not include the costs of liver transplantation or terminal care for the few thousand patients who will require that in the future. Also, such analysis does not even attempt to comprehend the economic impact of lost wages, home health care, loss of insurance, divorce, or other lifestyle changes required by the acquisition of a chronic disease. So the estimates of added hidden amortized health care costs for hepatitis and HIV are woefully inadequate. Most important, these estimates of cost simply avoid analyzing any cost that they consider controversial, such as the cost of immunosuppression. It may well be that immunosuppression, by contributing to length of hospital stay, secondary adverse outcome, and some mortality, is by far the most costly to our medical economy. If, for example, we accept the data from orthopedic surgery and find that postoperative infection is three times as prevalent in patients transfused allogeneic blood as autologous blood, then it is entirely reasonable to consider that allogeneic blood transfusion may be a significant cause of morbidity in these total joint patients (19). The costs of CMV infection have not been estimated or investigated and they may be substantial because more transfusions are used for transplantations and immunocompromised host. So with 22 million units of blood components transfused per year and costs from blood acquisition, transfusion, infection, and so on, it may be that the true cost of transfusion in health care today is between 25 and 50 billion dollars annually.

The United States is not self-sufficient in its blood supply (27). Some 2% of blood is imported, primarily from Western Europe. With approximately 285,000 units per year being *purchased,* assuming an acquisition cost of $50.00 (an estimate) per unit, that represents a 14.5 million dollar overseas expenditure just to support the United States' blood needs. In other nations where blood is a paid donation, the cost to the economy may be high as well.

In today's capitated care environment, the expenses for blood transfusion come directly from the total reimbursement fee paid to the hospital and physicians. Therefore, attention to truly indicated cost effective and necessary transfusion is one method of saving a hospital or practice considerable financial resources.

THE BENEFITS

The above discussion has summarized some data on risks of transfusion and costs. As stated at the beginning of the chapter, the transfusion decision is a risk–benefit ratio. On one side, there are (yet incomplete and constantly changing) data regarding the risks of transfusion. However, surprisingly little of the benefits of transfusion are known. To most clinicians, it might seem intuitive that when needed, patients appropriately transfused have improved outcomes. Yet any literature in support of such claims is hard to find. Transfusions are given to prevent anticipated adverse events. For coagulation components, the prevention or treatment of excess coagulopathic bleeding is a viable rationale for administration. However, the rationale for administration of red cells, although intuitively obvious, is hard to prove.

The threat of diminished oxygen-carrying capacity and its physiological consequences were discussed in Chapters 3 and 21. Tissue oxygen delivery is dependent on cardiac output and blood oxygen-carrying capacity (a product of

hemoglobin and its saturation plus physically dissolved oxygen in plasma). When reading historical literature regarding transfusion and outcome, the reader must be quite careful to separate hypovolemia from isolated euvolemic anemia. There is no doubt that anemia in the presence of hypovolemia is extremely detrimental. But anemia in the presence of normovolemia may be quite surprisingly tolerated (27–31). The lower limit of human tolerance for normovolemic anemia may be one definition of a transfusion trigger.

Unfortunately, the transfusion trigger (as just defined, the lower limit of euvolemic anemia) is not only not established in healthy humans but also probably extremely variable depending on disease states. In studies of acute anemia, the myocardium does not change its lactate flux until levels below 6g per dL are reached (31,32). Heart failure does not occur until the hematocrit drops below 10% (3.3 g per dL hemoglobin) (33). In animal models with varying models of coronary artery stenosis, the lactate flux reaction to anemia is extremely variable. Levels of 17% to 47% hematocrit have demonstrated myocardial ischemia in animal models (34,35). This author has experience with two patients, both young and healthy before surgery, who experienced extremely low levels of hematocrit and survived (one reached a hematocrit of 9% and the other, 3.6%). Both were Jehovah's Witnesses and refused blood transfusion, but with modem intensive care capabilities (surface cooling, mechanical respiration, extensive sedation, and muscle paralysis), neither developed myocardial, renal, or hepatic long-term sequelae of their severe euvolemic hemodilution. Therefore, what is the correct red cell transfusion trigger?

Clinical series with Jehovah's Witnesses and case reports show that levels of 6 to 8 g per dL of hemoglobin are routinely tolerated without any increase in mortality (28,36,37). In a review of multiple series of Jehovah's Witnesses involving some 1,404 operations, lack of blood and exsanguination caused only eight deaths or 0.6% and contributed to death in another 12 or 0.9% (28). That is a surprisingly small number. One might argue that those were all preventable by transfusion, but what we do not know is what other possible complications caused by transfusion were avoided in these 1,404 operations (28). Another statistical analysis of the outcome of Jehovah's Witness operations found that hemoglobin was not a significant predictor of outcome unless it was below 3 g per dL (38). Yet another article reviewing some 61 independent reports of Jehovah's Witnesses found 23 deaths due to anemia (0.48%) (27). Compare that with the suspected and computed risk of hepatitis transfusion in all patients transfused (perhaps 0.1% to 1%). If withholding all blood transfusion causes a mortality rate of about 0.5% and using blood in those as presently used causes hepatitis in 0.1% to 1 %, with multiple other morbidities and largely unknown mortalities, the issue of what is the appropriate transfusion trigger becomes even cloudier.

Patients with coronary artery disease or undergoing coronary artery bypass surgery might be considered to be at high risk for adverse outcomes of anemia and thus transfusion at a higher hematocrit than for healthy patients would therefore be warranted. One retrospective study with 27 patients (a small number) reveals that those undergoing peripheral vascular surgery were found to have a higher incidence of morbid events if their hematocrit dropped below 28% (14 patients) (39). Yet the group that had these events was older and underwent longer and more complex surgery than the other 13 patients without such events. Therefore, we are not able to conclude that in this high-risk patient group, a 28% or above hematocrit is necessarily the appropriate transfusion trigger. Another study of 30 patients who had multiple organ dysfunctions perioperatively showed no impact on oxygen consumption if their hemoglobin dropped below 10 g per dL (40).

Recent data from 2,202 patients undergoing coronary artery bypass grafting at 25 different centers throughout the United States actually showed a decrease in morbidity, myocardial infarction, and severe left ventricular dysfunction if their hematocrit was lower (less than 24%) on entry to the intensive care unit (41). Indeed intensive care unit entry hematocrit was the most important single variable in predicting adverse outcome in these patients, yet it was not confounded by patient risk or transfusion behavior. Also, in those with unstable angina, emergency surgery and reoperative coronary artery bypass (a high-risk group) showed substantially higher mortalities if their hematocrits were allowed to rise to 34% or greater as compared with 24% or below. Perhaps oxygen-carrying capacity and tissue oxygen delivery are not the only part of the story; rheology, platelet endothelial interactions, and other complex mechanisms may be at work. Once again, we are left with the question of when is it appropriate to transfuse and where should the transfusion trigger be in patients with preexisting disease. Various authors have discussed the state of the art in transfusion in subspecialty areas, and there are unique considerations in each of these presented. Yet not one can give a definitive answer of what is the appropriate transfusion trigger.

Indeed, to our knowledge, there is not a single publication in the world's literature supporting improved outcome with any given level of transfusion. There are no obvious clinical benefits to transfusion that have been proven, yet it seems so intuitively necessary. Wound healing has been promoted as better with transfusion and higher hematocrits, yet fibroblast activity requires only a low oxygen content and perfusion has been shown to be what is necessary, not any prescribed level

of hemoglobin or hematocrit. Subjective patient complaints of weakness or improved energy after transfusion have also been proposed in support of transfusion. However, where is the objective evidence? Any attempt to do a study regarding subjective feelings of wellness is fraught with inability to blind patients to receiving a transfusion. Transfusion carries such an emotional context with it that any patient infused with a red fluid might well feel better. Blood has widely been promoted as the life-giving force in an attempt to stir the public to donate. Therefore, if one is in the hospital and receiving of the life-giving force, how can any study be objective regarding a subjective assessment of feeling better. In the end, we are left with no objective data that transfusion of red cells at any one hematocrit improves outcome.

Yet 12 million red cell transfusions are given each year, some 60% of which are in the perioperative period. The decision-making process to transfuse should be based on a risk–benefit ratio for an individual patient. We know only some of the risks; we have no proven (objectively) benefits. Therefore, the decision must be made on an individual patient basis, guided by the best understanding of that patient's physiology.

Some organizations have tried to help in the guidance of the transfusion decision. In the 1980s, the National Institutes of Health (NIH) tried to change the practice and the nation by convening consensus conferences on red cell transfusion, platelet therapy, and the administration of FFP (42–44). In 1984, the American College of Obstetricians and Gynecologists published its recommendations regarding blood therapy (45). In 1990, the American Association of Blood Banks issued guidelines for blood therapy in patients undergoing coronary artery bypass grafting (46). In 1992, the American College of Physicians published red cell transfusion guidelines, and in 1994, the American College of Pathologists published guidelines for the usage of FFP, cryoprecipitate, and platelet transfusions (47,48). A, supplement to the *American Journal of Surgery* in December of 1995 contained the proceedings and conclusion of a consensus conference on blood management. Also in 1994, the American Association of Blood Banks published guidelines for appropriate review of blood utilization and also published consensus conferences on the use of autologous blood (49,50). Most recently, and appropriate for perioperative transfusion, the American Society of Anesthesiology has published its guidelines for blood component therapy (51). Indeed, there is a tremendous response from organized medicine in trying to guide the practitioner regarding transfusion decisions. All agree that the old transfusion trigger of 10 g per dL hemoglobin is outdated and incorrect. All seem to point toward individualization of the indication for transfusion and most agree that levels of 7 g per dL are well tolerated in otherwise healthy individuals.

The transfusion decision might be subcategorized into different clinical scenarios. Patients requiring in excess of five units and tending toward or requiring massive transfusion (one blood volume) clearly need a transfusion. There would be no argument and probably a great deal of survival data to suggest that blood improves outcome in this group. But no study will ever be done in support of that because it is immoral to conceive of not transfusing such patients. However, volume resuscitation is more important than hemoglobin, and once some transfusion has taken place, there is no need to expect better outcome with hematocrits in excess of 30%. Massive transfusions are relatively rare even in centers that perform hepatic transplantation, major complex cardiovascular surgery, or level 1 trauma (51). It is not so rare that they do not occur, but in one center doing level 1 trauma with more than 10,000 operations per year, the incidence of massive transfusion was only 125 times per year (51).

In patients transfused with somewhat less than five units, perhaps two to five units, the transfusion trigger and requirements become considerably more difficult to discern. Most clinicians may still agree that a transfusion was wise in these cases, but once again there may be more disagreement on how many units and what hematocrit to target either the beginning or end of transfusion. Again, one should be careful not to exceed 30% hematocrit because there is no indication for that.

Those patients receiving two or fewer units of transfusion might constitute an extremely large group of surgical patients. With a unit of red cells expected to increase hematocrit by approximately 3%, one has to wonder if there is any scientific expectation that morbidity or mortality would be improved at all in this group of patients. Perhaps this subgroup of patients might experience only the risk side of the transfusion equation. Once again, there are no data to examine such a question. The individual surgeon or anesthesiologist transfusing such a patient should take the greatest time and thought in examining exactly what is to be accomplished with a transfusion.

There is absolutely no support for an old transfusion guideline that if you are going to transfuse one unit, you should give two units. Clearly, two units represent twice the donor exposure and risk of one unit. However, if a unit of red cells can be expected to increase a normal patient (not on cardiopulmonary bypass) hematocrit by only 3%, one has to wonder when that single unit could truly improve oxygen-carrying capacity to the point of improving outcome. Once again, the individual clinician must ask the questions: What is to be accomplished by transfusing this single unit of blood? Is it to be given to increase a reserve of hematocrit in the anticipation of ongoing or future bleeding risk?

The indications for autologous blood harvest and transfusion are less clear. As the transfusion of choice, autologous blood avoids the risks of viral transmission, alloimmunization, and immunosuppression. But it is not totally risk-free, because of septicemia and clerical error. Because the risks to the patient from transfusion of autologous blood are reduced, it does make sense that this subtype of red cell transfusion should have different criteria for usage. Opinion differs on that subject, and some members of the NIH consensus panel voiced opinions that its indications should be the same as those for allogeneic blood. Perhaps the greatest risk is that a patient selected to be transfused and having only a portion of available units as autologous will receive allogeneic blood when his or her autologous blood is present. This does happen even in the best systems with checks and security measures. If a transfusion reaction, viral transmission, or other adverse event occurred in such a case, the event would seem particularly sad if the transfusion was triggered because of a liberalized transfusion trigger in anticipation of administering an autologous unit.

That is a hypothetical situation, but in the face of little data supporting the efficacy of transfusion one has to argue how can we liberalize transfusion triggers for autologous blood. If we support the liberalization of transfusion triggers, then we should be able to show or anticipate improved outcome in those with the more liberalized transfusion trigger. There are no published data to date to suggest that those patients receiving their autologous units do better than patients with a lower hematocrit/hemoglobin for like surgeries who did not receive any allogeneic blood. Perhaps it is easier on a case-by-case basis to face patients and families and explain that they received their autologous blood and therefore the added expense was not "wasted." Time and considerably more research will have to be done to settle the question of whether this practice of a liberalized transfusion trigger is correct for autologous blood.

With all of this production of august opinion and guidelines for therapy, there still exists an increasing demand for blood products. More astoundingly, there is a wide variability in practice. Nowhere is it more apparent than in cardiopulmonary bypass. In the early 1990s, data from 18 centers showed transfusion occurring in coronary artery bypass graft patients from 17% to 100% (52). A recent study in over 2000 patients at 25 centers showed that matching chest tube output to transfusion utilization had inappropriately high transfusion in 27% of patients (53). When surveyed by the American Association of Blood Banks, some 57% of physicians would have made inappropriate transfusion decisions (54). Physicians who were older or more removed from their training (residency) had a higher incidence of inappropriate transfusion decision-making. The literature is vast, and the recommendations are there regarding proper blood transfusion decisions. The public is demanding reform, and in Europe, officials are imprisoned for less than acceptable (in the public's view) decisions. Blood transfusion decision-making is serious business. It is made by the individual physician attaching the individual unit of blood to and infusion device or intravenous line. Each decision should be made with extreme care.

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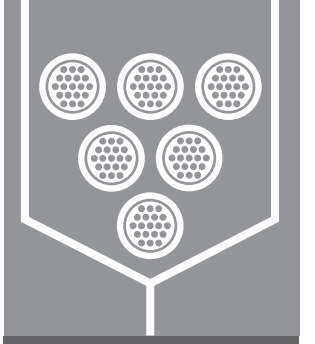

Undertransfusion

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Richard K. Spence ***Aryeh Shander***

The demonstration in the early 1980s that human immunodeficiency virus could be transmitted by blood transfusion awoke both the medical community and the public to the risks of allogeneic blood. National soul searching followed, leading to the promulgation of transfusion guidelines and the development of a culture of caution regarding blood transfusion. Patients became more hesitant to accept blood as the media publicized and often over-played the risks of transfusion (1). Finucane et al. (2) reported that the substantial majority of 1,204 people surveyed in 1997 and 1998 viewed the blood supply as risky and did not want transfusion. Bhopal et al. (3) found a similar result in the UK. Out of the 2,000 people surveyed, 62.3% believed that blood transfusion had a risk of HIV transmission.

Physicians were more reluctant to transfuse blood in the 1980s and 1990s than in the past, in part, because of a desire to cause no harm and in part, because of fear of litigation (4). As more blood-borne diseases such as new variant Creuztfeldt-Jakob disease (nvCJD) and West Nile virus appeared and the additional risks of immunomodulation and transfusion-related acute lung injury were defined, the desire to eliminate unnecessary and inappropriate transfusion gained more ground. Reports of successful treatment of patients without transfusion stimulated the growth of blood conservation and bloodless medicine and surgery programs that focused on reduction of allogeneic blood (5).

In the1980s and 1990s, hospital transfusion committees created and enforced more stringent hemoglobin transfusion triggers in part to protect themselves as outside regulators, e.g., Joint Commission on Accreditation of Healthcare Organizations (JCAHO), began to monitor transfusion practices. Maximum surgical blood ordering schedules (MSBOS) had had limited effectiveness in controlling transfusion because they only reduced the number of units *ordered*, not those actually transfused. The 1988 NIH consensus conference on red blood cell transfusion called for a clinical basis for transfusion and lowered the long-standing 10 gm per dL transfusion trigger to 7 to 8 gm per dL (6). Institution of these guidelines helped reduce *initial* transfusions by requiring pretransfusion hemoglobin of 8 to 9 gm per dL but there is no evidence of any impact on *subsequent* transfusion rates. In other words, once the trigger was pulled, the gun could be on automatic. There is good evidence that variability in transfusion practices persisted, as demonstrated by the European SANGUIS study and reports of cardiac and orthopedic surgery in the United States (7,8).

Some blood banks developed computerized tracking and reminder systems to follow both overtransfusion and undertransfusion (9,10). Using such a system, Gardner et al. (9) showed that undertransfusion was a *minimal problem*. Unfortunately, computers make transfusion recommendations based on predefined hemoglobin levels that are presumed to be clear indications of transfusion need, leading to transfusion decisions made in the lab rather than at the bedside where a patient's clinical status can be assessed. Moreover, these systems cannot assess true undertransfusion without clinical follow-up to determine adverse outcomes.

There is no question that individual patients and those grouped in certain diagnoses are transfused less than in the past for a variety of reasons. New technologies, such as the use of smaller volumes of asanguineous liquids to prime the heart–lung machine, have reduced the need for blood in cardiac surgery (11). Laparoscopic surgery requires precise identification and ligation of vessels and hemostasis from capillary bleeding. The result is diminished blood loss during surgery, thereby reducing transfusion for many procedures where it had been accepted practice (12,13). Blood loss is reduced in the majority of patients who have endovascular aortic grafting compared to open procedures (14,15). Orthopedic surgeons have reduced blood loss in joint replacement surgery through a combination of technical

improvement, antifibrinolytic drugs, and the substitution of autologous for allogeneic blood (16).

This practice of limiting transfusion prompted concerns in the blood banking community about the risks of undertransfusion. New information on risks of transfusion, scarcity of blood, and its rising cost has also raised a concern within the transfusion specialists community regarding inappropriate use of blood. Claude Lenfant (17) proposed in a 1992 letter to *Transfusion* that audits of transfusion practices for both undertransfusion and overtransfusion as a precautionary measure. Unfortunately, little was known about where to draw the line between the two. Overtransfusion had slowly grown from the 1950s to the 1980s. The development of surgical subspecialties such as cardiac, vascular, and orthopedic surgery relied on the ready availability of blood. It was not uncommon to hear surgeons referred to as *Bloody Bob*, or as "He's a good surgeon as long as he has a great blood bank!" Because traditional transfusion practice was anchored in the belief that blood was both relatively harmless and lifesaving, that is, that benefit outweighed the risks, physicians considered it safe to transfuse with impunity. For example, it was common practice to give two units of blood when one would suffice. The prevalence and risk of undertransfusion were unknowns.

Does undertransfusion occur? Our PubMed search of underuse *and* transfusion or undertransfusion produced a total of 14 references, suggesting that undertransfusion is rarely reported and /or rarely occurs. A search for misuse, inappropriate, or unnecessary transfusion produced 530 references. This latter group shed some light on undertransfusion. The Japanese Society of Anesthesiologists conducts an annual survey of life-threatening events in operating rooms in certified training hospitals. Causes are divided into four categories: those totally attributable to anesthetic management (AM), those resulting from preoperative complications (PC), those resulting from intraoperative pathological events (IP), and those related to surgical procedures (SP) (18). Analysis of SP-related deaths includes excessive surgical bleeding as a cause. The number of cardiac arrests was essentially the same between the 1980s and the 1990s (0.8% versus 0.88%), but deaths from SP-related causes decreased significantly from 21 cases in the 1980s to 6 cases in the 1990s (19). The authors state that this improvement was "probably due to proper treatment for massive bleeding," which strongly suggests that undertransfusion was not an issue (p140). Anesthesiologists at the University of Nebraska reviewed all perioperative cardiac arrests identified over a 10-year period from an anesthesia database of 72,959 anesthetics (20). Eighty percent of the arrests were related to medication errors, airway management, and technical problems with central venous access. Undertransfusion was not identified as a causative factor.

Pinkerton et al. (21) reviewed transfusion practices at Sunnybrook Health Science Centre in Toronto, focusing on changes from 1990 to 1997. Overall red cell transfusion had decreased by 18%, but rates had increased in oncology, trauma, and cardiac surgical patients. They attributed the decrease to more use of autologous predonation (45% of needs), fewer patients transfused, and fewer red cells given to each patient. They cite no evidence of harm from these practices, stating only concern as to when *adverse effects* will become apparent. Mair et al. (22) examined the records of 55 patients who had either a hemoglobin level <7 g per dL or a platelet count of $<10 \times 109$ per L. All except eight of the anemic patients received red cells and/or platelet transfusions. Reasons for not transfusing red cells included the patient's response to nutritional iron supplementation, refusal of blood, and noncompliance. Although this review shows that undertransfusion was not a problem, it also reveals that a hemoglobin-based trigger drove the transfusion decision, not clinical need (22). Kennedy's (23) review of transfusion guidelines at Ohio State University Hospitals versus actual practices failed to show evidence of harmful undertransfusion. The Texas Heart Institute saw no differences in outcomes for patients transfused only if hemoglobin dropped below 8 gm per dL (N = 212) when compared to those transfused to higher levels based on prevailing community practice (N = 216) (24). Saxena et al. (25) at the Los Angeles County–University of Southern California Medical Center calculated undertransfusion rates for RBCs and platelets over a 14-month period. One hundred forty-eight patients with a documented Hgb <5.0 gm per dL or a platelet count less than 10 x 109 per L did not receive transfusions within a 24-hour period after counts were measured. Of these, only one patient (1/148; 0.7%) in each group was determined to have not gotten a needed transfusion. Large scale studies of liberal versus restrictive transfusion strategies in critically ill patients demonstrated that more blood is not better and provided type one evidence that undertransfusion was not harmful (26).

Blood transfusion has been a mainstay in treating patients admitted with serious traumatic injuries. However, the percentage of these patients who receive blood is gradually decreasing, suggesting that evidence of undertransfusion might be found in the trauma literature. Farion et al. (27) reported that in 1995, 42% of their patients were transfused versus 54% of patients in 1991 ($p < 0.0001$) (27). Death from exsanguination is more a consequence of uncontrolled bleeding outside the hospital where transfusion is not available. Hemorrhage was responsible for 38% of deaths from trauma in patients treated at the University of California San Diego in 1988 (28). A similar mortality rate from exsanguination of 39% was recorded in 1992 in the Denver trauma system (29). The majority of these were

acute (48 hourrs; N = 81%)) and early deaths (2 to 7 days, N = 6%). The impact of transfusion or lack thereof is not reported. Exsanguination caused 30% of the deaths within the first hour after injury in Israeli Defense Forces killed in the June 1982 Lebanon War (30). Furthermore, 81% of deaths within the first four hours after injury were caused by hemorrhage. Blood transfusion was not readily available for these soldiers before evacuation to a base hospital.

Asensio et al. (31) performed a detailed analysis of predictors of outcome in the exsanguinated patient in their review of 548 patients treated from 1993 to 1998. Patients who met one or more criteria: (a) estimated blood loss > or = 2,000 mL during trauma operation; (b) required > or = 1,500 mL packed red blood cells (PRBC) during resuscitation; or (c) diagnosis of exsanguinations were included. Overall mortality was 379 of 548 (69%). Independent risk factors for survival in the emergency department were: penetrating trauma, spontaneous ventilation, and no ED thoracotomy (*P <0.001;* probability of survival 0.99613). Survival in the operating room was dependent upon ISS ,or 5 20, spontaneous ventilation in ED, operating room PRBC replacement <4,000 mL, no ED or operating room thoracotomy, absence of abdominal vascular injury (*P* ,0.001, max R (2) 0.55, concordance 89%). These data suggest that undertransfusion was not a factor in patient death, given the fact that mortality was higher in patients that received eight or more units of blood.

One can drill down further into trauma data to specific injuries associated with high blood loss to look for evidence of undertransfusion. Excessive mortality from bleeding during surgery of blunt hepatic injury has prompted a change to nonoperative management in these patients. Carmona et al. (32) analyzed 443 cases of liver trauma operated on at San Francisco General Hospital from 1976 to 1981. Overall mortality was 9% and most deaths were intraoperative (58%), with exsanguination as the primary cause of death. Mortality rates declined after they adopted a conservative, nonoperative approach to liver trauma. Investigators at the University of West Virginia found that the conservative, nonoperative management of blunt hepatic trauma in a rural environment reduced the use of blood. Patients treated between 1990 and 1995 received significantly less blood [10 units A versus 4.2 units B (*P* <0.0016)] than those treated between 1995 and 2000 (33). Furthermore, mortality was not increased with less blood, and both overall and ICU length of stay were actually reduced, suggesting that less blood (undertransfusion?) compared to an historical treatment standard was beneficial not harmful. Transfusion need is actually reduced with nonoperative management of hepatic trauma. Brasel et al. (34) treated 106 blunt hepatic trauma victims between 1991 and 1995 with either operative (14%) or nonoperative (86%) management. Transfusion requirements were significantly greater in the operative group versus the nonoperative (11.3 versus 2.7). The latter group also had significantly shorter intensive care unit stay and total LOS.

Only one study directly addresses the question of the impact of undertransfusion on outcomes. Gorman et al. (35) identified undertransfusion as a contributing factor of preventable deaths in a trauma population treated in North Wales. Forty-four of 1,088 trauma victims died from preventable deaths. Of these, 22%, or 10, were in nonhead injury patients. Of these, 38% or approximately four patients died from undertransfusion. Other contributing factors included missed injuries, (67%) poor airway care, (57%) delayed or no operation, (52%) and inadequate surgery (19%). This information is of limited value because of the small numbers, multiple potential confounders, and the absence of a detailed analysis.

Although the reported incidence of undertransfusion is low patients who die from hemorrhage represent a special population where unavailability of blood products and/or inability to keep pace with rapid bleeding may result in patients receiving fewer blood products than needed.

Although prospective data from critically ill patients suggests that a hemoglobin value of 7gm per dl is not associated with worse outcome and that liberal transfusion triggers are no better than restrictive ones, both U.S. and European transfusion practices still use an average hemoglobin of 8gm per dl as a threshold to transfuse. Is this because of the desire to eliminate inappropriate transfusion being countered by the fear that untreated significant anemia would lead to worse outcomes in those who might benefit from blood? The decision making process that leads to transfusion has been demonstrated to be variable at best. Whether or not the same variability exists when transfusions are withheld is unknown.

Identifying criteria for undertransfusion is as difficult as identifying those for transfusion. Most published data compare the presumptive risk of anemia to the known risk or assumed benefit of receiving an allogeneic transfusion, analyze the risk of no transfusion at all, or estimate the risk of anemia stratified by hemoglobin. Surveys of different surgical specialties fail to clearly demonstrate the true risk of anemia as it relates to morbidity and morality. Moreover, the risk to benefit ratio of transfusion is still unknown. Once these are defined, the risks of undertransfusion will become clear.

In summary, there is little convincing evidence that supports either the widespread existence of undertransfusion or creation of harm from limiting allogeneic blood use to appropriate clinical settings. In contrast, there is evidence that transfusion of less blood does no harm and may be beneficial. Therefore, we believe our focus should be on promoting *appropriate* transfusion practices that will further reduce both undertransfusion and overtransfusion.

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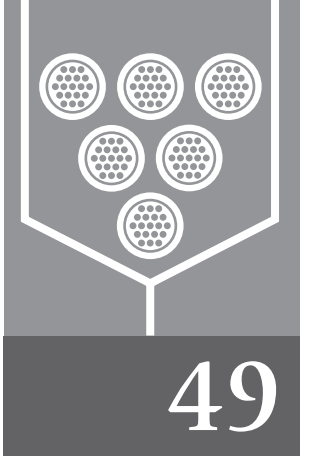

A Philosophy of Blood Management

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Aryeh Shander *Robert Spence* *Bruce Spiess*

Seventeenth and 18th century physicians were often known as philosophers, a name that reflected the approach to treatment they used. Some employed purgatives; others poultices; still others bloodletting. All too often this was a one-size-fits-all approach. We understand these philosophies today as derivatives of empirical observation in a time when there was little else to guide medical practice. Consider the distinguished American physician, Benjamin Rush, seeing clinical improvement in a patient with dropsy (congestive heart failure) after phlebotomy. He did not know that the bloodletting had decreased her preload and relieved the strain on her failing heart, but the anecdotal evidence of clinical improvement was enough for him. Consider, then, the impact of Rush's philosophy of bloodletting on another of his patients: George Washington, who died from pharyngitis, aggravated by the loss of three fifths of his blood volume through phlebotomy. In his case, the cure was most assuredly worse than the disease. These physician/philosophers can be forgiven for making the quantum leap from witnessing the benefit of bloodletting in a few patients to assuming that it must be good for all patients, just as we hope our predecessors will forgive us for cutting into patients.

Unfortunately, for many the clinical practice of blood transfusion remains mired today in this history of anecdotal evidence, received knowledge, and great expectations. Transfusion rates in identical procedures vary from hospital to hospital and from physician to physician; knowledge of risks of allogeneic blood is not widespread; guidelines for appropriate transfusion are not incorporated into physicians' practices, and when they are, they are often ignored. Mounting evidence today suggests that in many patients, allogeneic blood transfusion presents more risk than benefit. Moreover, many risks are known, measurable, and quantifiable while the benefit, presumed to be there, remains nebulous and anecdotal. Blood transfusion transmits the human immune deficiency virus (known risk). We can detect the virus in blood donors (measurable risk). We can calculate the risk by analysis of contaminated versus noncontaminated units (quantifiable risk), concluding that the risk of transfusion-transmitted HIV infection is one in two or more million units of blood. In contrast, what are the risks associated with performing an immunologically active, organ transplant, that is, an allogeneic blood transfusion? We know that the recipient's immune system is modified (known risk), but we do not know what the harmful outcomes are or how to measure them accurately. To err on the side of safety, we must assume that the *potential* risk of immunomodulation from transfusion exists in every unit of allogeneic blood and is additive as more units are transfused to the same individual.

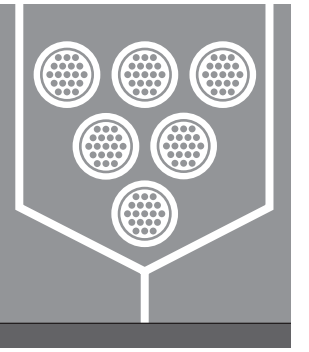
Even more worrisome is the lack of evidence about the actual benefits of allogeneic blood transfusion. Does it increase oxygen delivery? Increase oxygen consumption at the tissue level? Increase clotting capability? Increase circulating volume? All of these are reasonable expectations given the known properties of allogeneic blood, but their proof remains empirical and anecdotal. Do all patients benefit from blood transfusion (read: phlebotomy)? If so, when do they need blood (read: phlebotomy)? Although the benefit may be there, evidence of benefit as we speak of it in 21st century medicine simply does not exist.

The logical conclusion is that, until the benefit of allogeneic transfusions are well defined and the risk of this therapy is reduced on all fronts, to avoid risk we must avoid the use of allogeneic blood transfusion whenever possible,

while using other strategies that have been proven to offer benefit. The chapters in this text explore these alternatives in detail. We ask the reader to consider the following, underlying *philosophy* of blood management as he or she reads through the text.

1. Use clinical criteria, not a hemoglobin-based trigger, to guide your transfusion practice.
2. Evaluate every patient's potential risk for allogeneic blood transfusion well in advance of the time of need, then, consider how the use of alternative strategies can eliminate or reduce that need.
3. Always look at the patient first and the hemoglobin and hematocrit second.
4. Identify anemia early and correct it when possible.
5. Allogeneic blood transfusion is a living complex organ transplant, similar to a kidney or liver transplant in its immunological impact.
6. Consider that the risk you attribute to anemia in a patient may actually be the risk of its treatment—transfusion.
7. In invasive procedures, whether they are surgical or catheter-based, prevent bleeding and keep the blood in the patient.
8. Make the patient his or her *own* blood bank by using as many blood conservation techniques as possible.
9. Never waste blood—it is a precious resource.
10. Stop active bleeding! Stop it early!
11. If you must transfuse, use the safest available products following recommended guidelines one unit at a time.
12. Transfuse allogeneic blood one unit at a time, and then evaluate the benefit before proceeding.
13. Do not use cookbook orders for blood transfusion.
14. Respect the wishes and concerns of the patient, which means ask each patient about his or her concerns regarding allogeneic transfusion.
15. If you cannot transfuse, transfer. Do not allow a patient to suffer or die because of your fears about proceeding with treatment without the backup of a blood bank. Centers around the world are more than willing to help you in treating your patient.
16. Collect and share your data. Stay current. Teach others.

We appreciate the opportunity to bring this material to you and hope that you will share your experiences and questions with us. By working together, we can continue to build a new philosophy of blood management on sound evidence, not anecdotal evidence.



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