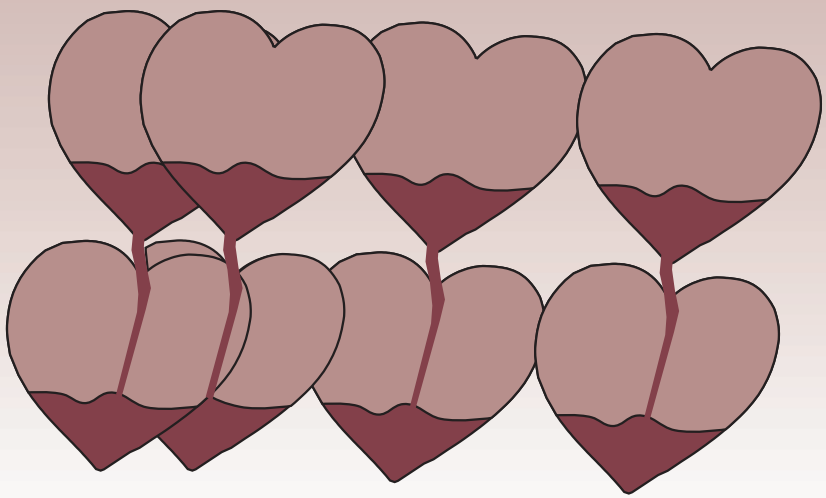
LANDES BIOSCIENCE Vademecum

Clinical Transfusion Medicine



Joseph D. Sweeney
Yvonne Rizk

v a d e m e c u m

Clinical Transfusion Medicine

Joseph D. Sweeney, M.D.
The Miriam and Roger Williams Hospitals
Brown University School of Medicine
Providence, Rhode Island

Yvonne Rizk, M.D.
Women and Infants Hospital
Providence, Rhode Island

LANDES
BIOSCIENCE
AUSTIN, TEXAS
U.S.A.

VADEMECUM
Clinical Transfusion Medicine
LANDES BIOSCIENCE
Austin

Please address all inquiries to the Publisher:
Landes Bioscience, 810 S. Church Street, Georgetown, Texas, U.S.A. 78626
Phone: 512/ 863 7762; FAX: 512/ 863 0081

ISBN: 1-57059-494-5

Library of Congress Cataloging-in-Publication Data

Sweeney, Joseph, 1952-
Clinical transfusion medicine / Joseph D. Sweeney, Yvonne Rizk.
p. cm.
"Vademecum."
Includes bibliographical references and index.
ISBN 1-57059-494-5
1. Blood--Transfusion handbooks, manuals, etc. I. Rizk, Yvonne. II. Title.
[DNLM: 1. Blood Transfusion Handbooks. WB 39 S974c 1999]
RM171.S926 1999
615'.39--dc21
DNLM/DLC 99-24311
for Library of Congress CIP

Contents

Section C: Medicine

Preface

Clinical transfusion medicine is an evolving subspecialty, which straddles traditional areas of pathology and clinical hematology. This subspecialities is concerned with aspects of blood procurement, including safety, logistics and economics, and the appropriate use of blood products in different clinical situations. This causes the transfusion medicine physician to interact with (and occasionally come into conflict with!) surgeons, anesthesiologists, internists, and many subspecialists in internal medicine, particularly, oncologists and hematologists. The resultant of this interaction should be improvement in blood utilization. In short, the role of clinical transfusion medicine is to promote good transfusion practice.

Promoting good transfusion practice is often hindered by a lack of good clinical data validating many current transfusion practices. Confounding this problem is the often entrenched belief in the clinical usefulness of many traditional transfusion practices. The transfusion medicine physician is, therefore, frequently put in the position of altering practices, a precarious role in any institution!!

This short book is intended to put clinical problems in perspective as they relate to decision making regarding blood transfusion. It is aimed at nursing staff, perfusionists, nurse practitioners, physician assistants and medical students and residents, many of whom lack depth in their understanding of transfusion. The language is kept as nontechnical as possible therefore, and detail is intentionally omitted. However, it is hoped that the background information and general principles should facilitate the exercise of good judgment.

Joseph D. Sweeney, M.D.
Yvonne Rzik, M.D.
Providence, Rhode Island
May, 1999

Acknowledgments

The expert assistance of Ms. Susan Sullivan in the preparation of this monograph is gratefully acknowledged.

1 Introduction

The scope of transfusion medicine can be separated into two definable areas of activity (Fig. 1.1). First, there are those activities concerned with the *manufacture of blood products*. These processes occur mostly in Community Blood Centers or Fractionation plants. The 'source material' is obtained from healthy human subjects, known as blood donors. This part of transfusion medicine is concerned with the collection, processing, and testing of blood donations and the maintenance of an inventory of blood products prior to shipping to sites of transfusion. The kinds of activities are similar to those which occur in standard pharmaceutical houses. Emphasis is on the potency, safety, efficacy, and purity of the manufactured blood products.

The second area of transfusion medicine can be described as *clinical transfusion medicine*. Clinical transfusion medicine is concerned with aspects related to the transfusion of blood products to recipients. The human subjects of interest are sick patients, and called blood transfusion recipients. Emphasis is on product availability, appropriateness of use, informed consent, compatibility testing, administration of blood, monitoring for adverse events (called transfusion reactions) and the long term follow up for complications of infectious disease. These differences are shown in Table 1.1 but are really a continuum, as illustrated in Figure 1.1.

This book is concerned with the second area of transfusion medicine i.e., clinical transfusion medicine. Brief reference will be made to manufacture, however, where background information is important. Clinical transfusion medicine mostly occurs in a hospital setting, although other sites of transfusion are becoming commonplace, such as outpatient departments, renal dialysis units, physician offices or even the recipient's home. Within the hospital structure, the focal area for this activity is the blood bank. Although blood banks are concerned with the dispensing of a therapeutic product, they are often part of pathology laboratories. From a theoretical perspective it would be more appropriate if blood banks were more closely linked to hospital pharmacies. A comparison of pathology laboratories, blood banks, and pharmacies in Table 1.2 illustrates this point. The historical reason for blood banks to be within departments of pathology, and not part of a pharmacy, primarily relates to the need to perform compatibility testing as this testing is similar to other kinds of tests traditionally performed by laboratory technologists.

The purpose of this book is to serve as a quick source of useful, practical information for the many aspects of clinical transfusion medicine. The content reflects practice in the United States, but is generally applicable to other countries. Knowledge of transfusion medicine is surprisingly limited even among experienced hematologists and pathologists and a simple rapidly readable text serves a useful

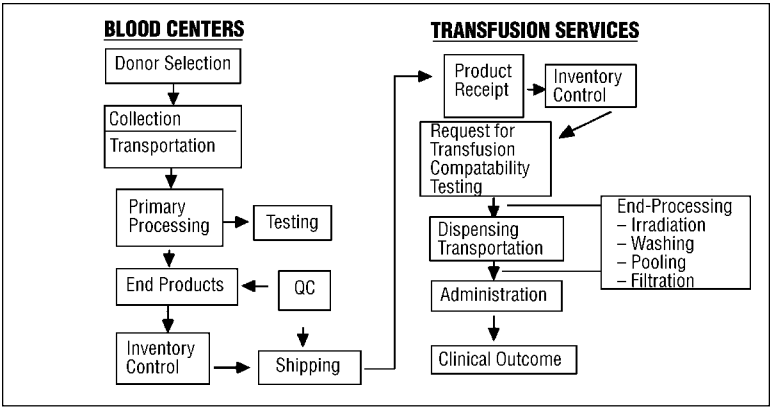


Fig. 1.1. Activities in blood centers and transfusion services. Product quality is the focus of blood centers; clinical outcome is the focus of transfusion services.

Table 1.1. Comparison of the major areas of activities in transfusion medicine

	Manufacture of blood products	**Clinical transfusion medicine**
Site	Blood center or plasma fractionation plant	Blood bank/ transfusion service
Activity	Manufacture of blood components and derivatives	Transfusion of blood components and derivatives
Regulatory agencies/ accrediting (USA) organizations	FDA AABB CAP	JCAHO AABB
Product specifications	Defined	General terms
Variation in practices between sites	Minimal	Large variations in techniques/and practices
Auditing of practices	Standard performed	Variable; often not
Human population	Healthy subjects (blood donors)	Ill Subjects (blood recipients)
Product focus	Potency; efficacy; safety; purity;	Availability; appropriateness of use and administration effectiveness adverse events

FDA = Food and Drug Administration
AABB = American Association of Blood banks
JCAHO = Joint Commission on Hospital Accreditation
CAP = College of American Pathologists

Table 1.2. Comparison of diagnostic pathology laboratories, blood banks and pharmacies

	Pathology Laboratories	Blood banks	Pharmacies
Product	Diagnostic	Therapeutic	Therapeutic
Personnel	Technologists/	Technologists/ Technicians	Pharmacists Technicians
Specialist Physicians	Pathologists	Pathologists/ Hematologists	Clinical Pharmacologists
Regulatory/ Accrediting Agencies	CAP; JCAHO	CAP; AABB; JCAHO; FDA	JCAHO; FDA

CAP = College of American Pathologists; AABB = American Association of Blood banks JCAHO = Joint Commission on Hospital Accreditation; FDA = Food and Drug Administration

need. It is divided into sections, each consisting of short chapters which can be read within five minutes addressing specific clinical situations, and facilitation of rapid clinical decision-making or giving essential background information are the objectives of the book. It is not intended as a reference text in transfusion medicine, therefore, and the readership is aimed at medical students, residents in training, or nursing and allied health personnel. Chapters are, therefore, intentionally short without specific references. When more detailed information on a specific clinical situation is required, it is suggested that an electronic search be conducted or reference textbooks such as may be conveniently available in the Blood bank should be consulted. Suggested sources of information with more detail are given in the Appendix.

Allogeneic Blood Products

The term *allogeneic* refers to blood products manufactured from blood donations from healthy subjects (blood donors) which are intended for transfusion to different subjects (blood recipients). In the past these products were called "homologous", but the current preferred term is allogeneic, in order to be consistent with solid organ transplantation terminology. Other names used regionally to describe these products are; "regular blood", "shelf blood" or "banked blood".

The term Blood Product, then, is an all embracing term used to describe any end-product produced from human blood. First, there is *whole blood*, which is collected into a solution that functions both to anticoagulate and preserve the red blood cells. These are simple solutions containing citric acid to chelate calcium and, therefore, prevent activation of the coagulation system and glucose to allow red cells to metabolize during in vitro storage (e.g., citrate-phosphate-dextrose or CPD). Adenine may also be present (CPD-A1), which improves red blood cell adenosine triphosphate (ATP) levels. Anticoagulated whole blood is collected into, stored in, and transfused from, its primary container. Although whole blood was commonly used prior to the 1970s, this has diminished over the past decades. The two remaining clinical situations where whole blood is still preferentially requested for transfusion are patients with trauma requiring multiple transfusions and cardiac surgery, particularly pediatric cardiac surgery. This is because it has been suggested that 'fresh' whole blood (less than 48 hours old) may be preferable to correct any coagulopathy which may develop in these patients . However, the practical logistics of having fresh whole blood routinely available makes this difficult to achieve in practice.

Second, most whole blood donations are further processed by centrifugation into a number of *blood components*. Each whole blood donation is capable of producing up to five different components, but commonly, either red blood cells and plasma, *or* red cells, plasma and platelets are produced. Further processing of a unit of plasma can produce a unit of cryoprecipitate and a cryosupernatent, the latter known as cryo poor plasma. Some fibrin glue preparations are similar to cryoprecipitate, except that the process may be modified to enhance fibrinogen yields (see Chapter 23). In practice, almost all allogeneic whole blood donations are processed into at least two components, such as a red cell concentrate and plasma. The red cell concentrate can be stored in the anticoagulant plasma alone (CPD red blood cells; CPD-A1 red blood cells), or a crystalline solution can be added, which contains glucose and stabilizers to maintain the quality of red cells during the storage period (Adsol®, Nutricell®, or Optisol®). The maximum duration of storage for red cells (at 1-6°C) under such circumstances is currently 42 days (Chapter 27). Much of the plasma produced from the whole blood dona-

tions is shipped to fractionation plants for further manufacture into blood derivatives. Some of the plasma, however, is retained in blood centers in the frozen state and used for clinical transfusion purposes (see Chapter 29).

A single unit of platelets may also be produced from each blood donation. Although the terminology is confusing, a platelet unit derived from a whole blood donation is commonly known as a random donor platelet. A separate type of blood component is an apheresis blood component. Several different types of apheresis components are available but the most important is the platelet apheresis product, commonly known as single donor platelets. As indicated above, a unit of random donor platelets is also derived from a "single donation" and hence the terminology is confusing (Chapter 28). Other allogeneic apheresis products may be more widely available in the future, as a 'double unit' of red cells, or combinations of platelets and red cells, or red cells and plasma, may be obtained from a single donor using these devices. It is anticipated that many such products will be approved for use by late 1999. The hallmark of a blood component is that is derived from a single donation. Each such donation has a unique identification (unit number or lot number).

Third, there are blood products known as *blood derivatives*. These are manufactured from a plasma pool usually containing between 5,000 and 20,000 donations. This plasma pool constitutes a new lot number, composed of the individual lot numbers of each donation which makes up the pool. All blood derivatives in current use are acellular products. Derivatives in common use are 5% or 25% albumin, immunoglobulins, and the plasma derived coagulation factor concentrates. Since blood derivatives are produced from such a large number of blood donations, there is always the ongoing concern that new viruses from apparently health donor(s), may enter each pool and potentially infect a large number of recipients. This was responsible for the spread of hepatitis in the 1970s and, subsequently, human immunodeficiency virus (HIV-1) in the 1980s in the hemophilic population. Blood derivatives are routinely subjected to a variety of processing steps. Some of these steps are intentionally performed to destroy viruses, which is called *viral attenuation*. Use of at least two different types of viral attenuation processes is now common in order to optimize the destruction of viruses. Examples of these processes are pasteurization i.e., heating to 60°C for ten hours; various separation steps, e.g., gel filtration or micro-filtration, and chemical treatments such as solvent detergent exposure. In spite of the clear effectiveness of these viral attenuation processes, there is still the potential for some viruses to be resistant to these steps and result in the infection of blood transfusion recipients.

The last type of allogeneic blood product is stem cell products. Stem cells can now be collected from a number of sources, other than the traditional bone marrow, such as peripheral blood or umbilical cord blood. Allogeneic stem cell products are always derived from a single donor, but multiple donations may be required if peripheral blood is the source. Since stem cells are generally transfused in specialized transplant units, they will not be described further and the reader is

referred to the *Clinical Handbook of Bone Marrow Transplantation* for further information on these products and associated technology. These products are illustrated in Figure 2.1.

The physical state of blood products during storage varies with the product type. Red cells and platelets are typically stored in the liquid state. Plasma and cryoprecipitate are stored in the frozen state. Certain blood products are manufactured and stored in the lyophilized state; examples are some immunoglobulin preparations and coagulation factor concentrates. However, red cells (or less commonly platelets) may also be stored in the frozen state using cryoprotective agents; and certain blood derivatives, such as one preparation of immunoglobulin and all albumin preparations, are stored in the liquid state. All products are transfused as a liquid product, either after thawing of frozen products or reconstitution of lyophilized products. This accounts for the delay in availability since it takes between 15-30 minutes to either thaw frozen products, or to reconstitute lyophilized products prior to transfusion. This is shown in Table 2.1.

The allogeneic blood supply in the United States, much of Europe and Japan is predominantly collected from what are known as 'volunteer blood donors'. These donors donate for altruistic reasons and do not receive any remuneration or reward of a material monetary value. Platelet pheresis donors in some centers receive a token remuneration. However, much of the plasma collected for fractionation comes from paid donors. A different type of volunteer blood donor is known as a directed donor, and the donation as a 'directed donation'. Directed donor blood products are allogeneic blood products which meet all the requirements for

Source:	Healthy Humans Donors Donation (= individual lot #)	
Products:	Whole blood (single donation)	
	Blood components (single donation)	Red Blood Cells -plasma → cryoprecipitate; cryo poor plasma -platelets -apheresis components
	Blood Derivatives (5,000-20,000 donations)	Albumin Immunoglobulins Coagulation Factors
	Stem Cells (single/multiple donations)	Bone Marrow Peripheral Blood Umbilical Cord Fetal Hepatocytes
Physical State	Liquid (e.g., red cells, platelets) Frozen (e.g., plasma) Lyophilized (e.g., derivatives)	

Figure 2.1. Allogeneic blood products

Table 2.1. Some properties of allogeneic blood products in common use

Product	Physical State	Approx. Volume (mls)	Storage Temperature	Shelf Life	Comments
Whole blood in CPD	Liquid	525	1-6°C	21 days	Hematocrit approx. 35
Whole blood in CPD-A1	Liquid	525	1-6°C	35 days	Hematocrit approx. 35
Red Blood Cells in CPD	Liquid	300	1-6°C	21 days	Hematocrit < 70
Red Blood Cells in CPD-A1	Liquid	300	1-6°C	35 days	Hematocrit < 70
Red Blood Cells in Preservative	Liquid	350	1-6°C	42 days	Hematocrit 50-60; little plasma
Random Donor Platelets (RDP)	Liquid	50	20-24°C	5 days	4-10 units pooled into a single container
Single Donor Platelets (SDP)	Liquid	180-350	20-24°C	5 days	Equivalent to 6-8 units of RDP
Fresh Frozen Plasma	Frozen	220	-18°C or lower	1 year	15-30 minutes to thaw
Cryoprecipitate	Frozen	5-15	-18°C or lower	1 year	Thawed, then pooled
Vial of Coagulation Factor	Lyophilized	10-20	Refrigeration	1 year	Reconsti-tuted with diluent, then transfused

CPD = Citrate – Phosphate – Dextrose
CPD-A1 = Citrate – Phosphate – Dextrose – Adenine

a standard allogeneic blood product. However, they differ in that the intended recipient is identified at the time of donation. The practice of directed blood donation is often performed in the context of donating blood for a relative or friend in anticipation of surgery or cancer chemotherapy. Directed donations are generally neither encouraged nor discouraged by blood collection facilities. There is no evidence that they are any more safe (i.e., less likely to transmit viral infections)

than the non-directed volunteer blood supply. On the contrary, since many directed donors are first time donors, there is a higher prevalence of viral disease markers, raising concern regarding a possible increased risk. Directed donor blood may be transfused to a recipient other than the intended recipient, if the latter does not require transfusion, a practice *"called crossover"*.

All allogeneic blood donations are routinely tested for syphilis and viral disease markers as shown in Table 2.2.

Table 2.2. Testing of blood donations for microbial diseases

Test	**Year Initiated**
Serological Test for Syphilis	1949
Hepatitis B Surface Antigen (HBs As)	1972
Antibody to HIV-1	1985
Antibody to Core Antigen of Hepatitis B (Anti HBc)	1986
* Alanine Aminotransferase (ALT)	1986
Antibody to HCV	
Generation I	1990
Generation II	1992
P24 Antigen of HIV-1	1996
Nucleic Acid Testing for HCV, and HIV-1	1999

* No longer routinely required

Autologous Blood Products

3

Autologous blood products differ from allogeneic products in several important respects. First, the source of the product may not always be a healthy human donor but rather, a patient with an anticipated need for blood products in the near or immediate future. Second, criteria for accepting blood donations in most collection sites differ between allogeneic and autologous blood donors, with more liberal criteria being applied to autologous donors. Third, the autologous blood donation is a special type of directed blood donation in that the donor is the intended recipient and unlike directed donor units, it is an uncommon practice to use autologous units for transfusion to a recipient other than the intended recipient (crossover, Chapter 2). Fourth, autologous products differ substantially from allogeneic products in composition, potency and shelf life. Different types of autologous products and some characteristic features are shown in Figure 3.1.

PREDEPOSIT AUTOLOGOUS BLOOD (PAD)

This type of blood product most closely resembles the standard allogeneic whole blood donation. The blood may be collected and retained as a unit of unprocessed whole blood, but it is much more common to process the donation into a unit of red blood cells and plasma. The red cells are often stored in an additive solution, which extends the shelf life to 42 days (see Chapter 2). The disposition of the plasma varies. It may be made available for use by the autologous donor. It is also possible to ship this plasma to fractionation plants, if the autologous blood donor meets all the standard criteria for allogeneic blood donation. Occasionally, the autologous plasma can be used to manufacture cryoprecipitate or a fibrin glue concentrate for intraoperative use, for example, in vascular or cardiac surgery.

Predeposit autologous blood (PAD) is donated within the six week period prior to intended use, but most commonly within 3-4 weeks of surgery. It is the most common form of autologous blood product. Units are collected generally at weekly intervals, but at not less than three day intervals, and not within 72 hours of the intended time of surgery. These products are tested for standard infectious disease markers, as in the case of allogeneic units (Chapter 2). An important difference, however, is that the presence of a positive infectious disease marker tests (which always precludes the shipping of an allogeneic blood product), may allow the shipping of the autologous units for transfusion. Such units will have a biohazard label attached. Suitable patients for PAD are shown in Table 3.1.

Rarely, platelets are donated in a predeposit context, using apheresis devices, and under these circumstances, the platelets are cryopreserved. The only practical use of this *uncommon practice* is in the management of patients in remission of

Clinical Transfusion Medicine, by Joseph D. Sweeney and Yvonne Rizk. © 1999 Landes Bioscience

Procedures and Types of Products	Component	Volume (mls)	Shelf Life
(a) Predeposit Autologous Donation: (PAD)	Whole blood Red Cell Component Sometimes Plasma/ Cryoprecipitate or (fibrin glue) cryo-preserved platelets	525 350	35 days 41 days
(b) Preoperative Hemodilution: or Preoperative Apheresis	Whole blood Platelets Plasma	475-565 180-400	8 hours 8 hours
(c) Intraoperative Salvage (Processed or Unprocessed)	Red Blood Cells	variable	8 hours
(d) Post Operative Salvage	Red Blood Cells	variable	?
(e) Stem Cell Products	Bone Marrow Peripheral Blood		

Physical State:
Liquid (Red Cells/Platelets)
Frozen (Plasma/Cryopreserved Platelets)

Fig. 3.1. Autologous blood products; Source: patients requiring surgical/medical treatment

Table 3.1. Patients suitable and unsuitable for predeposit autologous donation

I. Elective
1. Orthopedic or urologic surgery
2. Elective vascular or cardiac surgery
3. 'Elective' abdominal procedures (e.g. colorectal surgery)

II. Performed primarily to allay anxiety, but unlikely to be of value
1. Obstetrical patients
2. Prior to minor cosmetic procedures or minor surgery (e.g. lumpectomy)

acute myelogenous leukemia, in anticipation of use during consolidation therapy or subsequent bone marrow transplantation.

PREOPERATIVE HEMODILUTION OR PREOPERATIVE APHERESIS

Preoperative hemodilution or preoperative apheresis is essentially the same type of procedure. Anticoagulated blood is collected immediately before (i.e., within 2 hours) a surgical procedure. The end product of preoperative hemodilution is a

unit of unprocessed whole blood in CPD as anticoagulant. Preoperative apheresis is a procedure in which blood components, most commonly platelets, but sometimes plasma, are collected preoperatively with the intention of transfusion, usually towards the end of the surgical procedure. Examples of components collected in this category are platelets collected prior to cardiac surgery with the intent of reinfusion immediately subsequent to protamine neutralization; or plasma collected preoperatively and reinfused in the same situation. These apheresis autologous products have also been used in orthopedic and vascular surgery, although this is not as well studied. In addition, although the intraoperative time period is short, plasma collected preoperatively can be processed further in the operating room into a fibrin glue preparation, using special devices, which are capable of rapid freezing and thawing. Preoperative hemodilution, and particularly preoperative apheresis, are not standard in many surgical centers. The types of patients who are candidates for this procedure are similar to those who predeposit autologous blood, i.e., patients undergoing elective orthopedic, urologic or vascular surgery, and cardiac patients who are unsuitable for predeposited autologous donation (Table 3.1).

INTRAOPERATIVE SALVAGE

An autologous blood product can also be produced from red blood cells which are salvaged (i.e., collected) intraoperatively from a site of surgical bleeding site. Red blood cells, which are shed from the surgical field, are anticoagulated and collected into a reservoir. Anticoagulation is achieved by adding heparin to the reservoir or by the addition of citric acid concurrent with aspiration. When the blood in the reservoir achieves a critical volume (600 to 800 ml), the aspirated blood can be returned to the patient, either as unprocessed blood using a filter or as processed red cells, usually using a washing technique. Unprocessed salvaged blood collected is simpler, but there is always concern with regard to contaminating cellular debris, particulate matter or activated clotting factors. Washing devices operate on the principle of centrifugation and the end product is composed of autologous red cells suspended in saline, with a volume of approximately 250 ml and an Hct of 40-60. These red cells are returned to the patient intraoperatively, if possible, or in the immediate postoperative period. All such returned blood is routinely filtered to remove white cell clumps and large particulate matter. If transfused outside of the operating room, proper identification of the unit and a written expiry time is critical. Patient populations suitable for this procedure are shown in Table 3.2.

POSTOPERATIVE SALVAGED BLOOD

A different type of blood product is that derived from postoperative salvage. This is most often collected from drainage sites after orthopedic surgery or from