Chapter 38
Transfusion of Blood and Blood Products

In transfusion medicine, several blood products can be prepared and used as replacement therapy; however, four of these products are more commonly used in general practice: RBCs, fresh frozen plasma (FFP), platelets and cryoprecipitate. RBC transfusions are mainly administered to improve tissue oxygenation in cases of anaemia or acute blood loss due to trauma or surgery. FFP, platelets and cryoprecipitate are used for the prevention and treatment of bleeding.

Red Blood Cell Transfusions

Red blood cell transfusions have been the standard of care for treating anemia for more than 100 years. Approximately 15 million units of red blood cells (RBCs) are transfused annually in the United States, and about 85 million units are transfused annually worldwide [1–3]. Historically, patients have been transfused when the hemoglobin level fell below 10 g/dL [4]. The 10/30 transfusion trigger has been ascribed to a paper by Adams and Lundy published in 1941 [5]. In this paper the authors made the following recommendation "*when concentration of hemoglobin is less than 8–10 g/100 cm³ of whole blood, it is wise to give a blood transfusion before operation*" [5]. The 10/30 transfusion trigger was widely accepted without supporting evidence from clinical trials. Over the last two decades the transfusion trigger has drifted down as RCTs have failed to demonstrate a benefit from the 10/30 trigger.

Anemia is common in critically ill patients. More than 90 % of patients have a "subnormal" hemoglobin concentration by the third day of ICU admission. The etiology of anemia of critical illness is multi-factorial and complex. Decreased production of erythropoietin (EPO), impaired bone marrow response to erythropoietin, reduced red cell survival as well as blood loss from repeated phlebotomies and surgical procedures have been implicated in the anemia of critical illness. Despite the fact that blood transfusions have not been shown to improve the outcome of ICU

Table 38.1 Effect on oxygen delivery (DO_2) by increasing cardiac output, PaO_2 or hemoglobin by 20 %

Hemodynamic variable	20 % increase	% increase in DO_2
Cardiac output	5–6 L/min	18 %
PaO_2	60–72 mmHg	6 %
Hemoglobin	10–12 g/dL	18 %

patients (discussed in detail below) and that the current guidelines only recommend blood transfusion when the hemoglobin falls below 7.0 g/dL, almost half of all patients admitted to an ICU receive a blood transfusion [6, 7].

Why Transfuse?

$$DO_2 = CO \times \left[\left(Hb \times Sat \times 1.34 \right) + 0.031 \times PaO_2 \right]$$

As is evident from the oxygen delivery equation (DO_2) one of the most efficient means of increasing oxygen delivery to is increase the hemoglobin concentration (see Table 38.1). Therefore, the obvious indication to transfuse blood would be too increase oxygen delivery which should then theoretically increase tissue oxygen tension and tissue oxygen utilization. Unfortunately there is little data to support this concept and it is likely that blood transfusion increases oxygen utilization only in patients with a hemoglobin of less than 4 g/dL…. Yes that is right, less than 4 g/dL [8, 9]. A number of studies in critically ill patients have measured oxygen consumption before and for up to 6 h following a blood transfusion. All of these studies have failed to demonstrate an increase in tissue oxygen tension and oxygen utilization following blood transfusion [10–12]. Indeed, paradoxically (dependent on the age of the transfused cells), red blood transfusions may compromise tissue oxygenation.

Risks Associated with Blood Transfusion (See Fig. 38.1)

For much of the last century RBC transfusion has been viewed as having obvious clinical benefits and blood transfusion was considered as a lifesaving strategy [5]. However over the last 20 years RBC transfusion practice has come under increased scrutiny. Initially this was driven by concerns over transfusion related infections, HIV in particular. While the risk of transfusion transmitted infections has received considerable attention, the risks of this complication with modern blood banking techniques is now exceedingly remote [13]. On the other hand, it is now becoming clear that there are other important, less recognized risks of RBC transfusion related to RBC storage effects and to immunomodulating effects of RBC transfusions which occur in almost all recipients [14, 15]. The risks of blood transfusion include
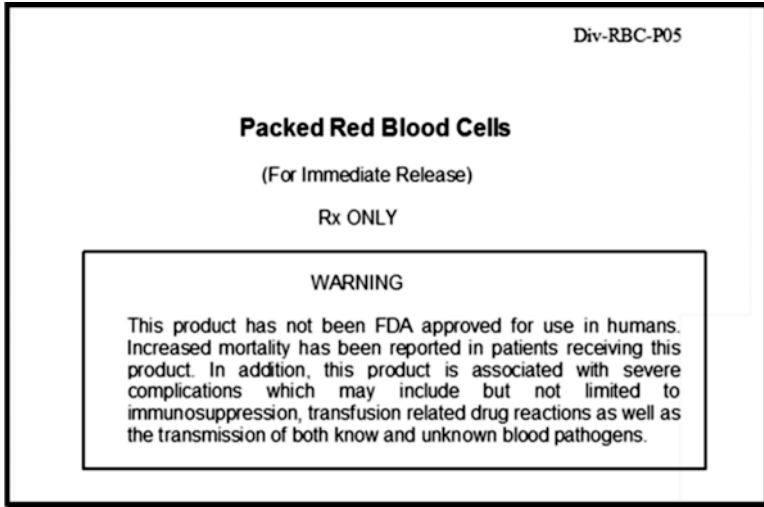
Fig. 38.1 Blood products do not have a package insert. If a package insert did existed for packed red blood cells it would probably be accompanied by a black box warning as suggested in this figure [15–17]

both infectious and non-infections complications; these are listed below [16]. Several strategies such as leukoreduction and shorter storage times (still under investigation) have been employed to reduce transfusion complications. However, the most obvious approach to reduce transfusion-related complications is to reduce the number of transfusions administered.

Risks Associated with Blood Transfusion

Infectious

- Human immunodeficiency virus (HIV)
- Hepatitis B, C, D
- Cytomegalovirus
- Parvovirus B19
- Epstein–Barr virus
- Human T cell leukemia/lymphoma virus
- Human herpes virus 6, 7 and 8
- Toxoplasmosis
- Malaria
- West Nile virus
- TT virus
- Prion disease?

Noninfectious

- Immune activation
  - Non-hemolytic febrile reactions
  - Anaphylactoid allergic reactions
  - Acute hemolytic reaction
  - Delayed hemolytic reactions
  - Transfusion related acute lung injury (TRALI)
  - Delayed TRALI syndrome
  - Transfusion associated graft versus host disease
- Immune tolerance
  - Nosocomial/postoperative infections
  - Multi-organ failure
  - Transplant tolerance
  - Cancer recurrence?
  - Auto-immune disease
- Activation of clotting
  - Increased risk of acute coronory syndrome
  - Increased risk of thromboembolic disease
  - Increased risk of arterial thrombosis
- Proinflammatory
- Increased oxidative injury

Complications associated with massive blood transfusion (>10 units in 24 h)

- Citrate toxicity
- Hypocalcaemia and hypomagnesaemia
- Hyperkalemia
- Hypothermia
- Coagulopathy

Transfusion-Associated Immunomodulation

Transfusion related immunomodulation (TRIM) occurs to some degree in almost all recipients of blood and blood products and are the cause of most of the complications associated with blood transfusion [14]. Clinical evidence for the existence of TRIM was first reported in 1973. Opelz and colleagues provided evidence that allogenic blood recipients had improved renal allograft survival [18]. This observation was subsequently confirmed in prospective clinical trials [19]. TRIM may result in either immune activation or immune suppression, this being dependent on the interaction between host and donor factors. Clinical syndromes associated with immune activation in the recipient include a variety of transfusion reactions including febrile non-hemolytic transfusion reactions (FNHTR), transfusion associated graft-versus-host disease (TA-GvHD), transfusion related acute

lung injury (TRALI), alloimmunization and possible development of various autoimmune diseases. Syndromes associated with tolerance induction and immunosuppression include increased predisposition to nosocomial and postoperative infections, cancer recurrence, microchimerism and enhanced survival of various allografts in recipients.

While TRIM appears to be a ubiquitous phenomenon the mechanisms leading to immunomodulation remains poorly understood. A number of mechanisms have been proposed relating to the transfusion of donor antigen presenting cells (APC), donor stem cells (leading to microchimerism), donor white blood cells, donor immuno-globulins, donor cytokines from activated WBC's and iron and free hemoglobin from hemolyzed red blood cells. It is likely that these mechanism act in concert to alter the immune status of the host. Allogenic blood transfusions introduce a multitude of foreign antigens including HLA-class II bearing donor dendritic antigen presenting cells (APC) in recipients. Blood transfusions induce TRIM in two opposite ways causing either i) allo-immunization or ii) tolerance induction. Immunization is reflected by the induction of HLA alloantibodies and T cell activation, while the induction of tolerance is suggested by enhanced renal, hepatic, cardiac, pancreatic and skin allograft survival in transfused versus non-transfused recipients. Presence or absence of "autologous" HLA-DR Ag on the leucocytes of the transfusion donor plays a decisive role whether immunization or immune suppression will ensue following allogenic blood transfusion [20]. Transfusions sharing at least one HLA-DR antigen with the recipient will induce tolerance while fully HLA-DR mismatched transfusions lead to immunization. Accumulation of various soluble bioactive substances occurs during storage and includes histamine, lipids, cytokines, fragments of cellular membranes, soluble HLA class I antigens, many of which are WBC derived and play an important role in TRIM. TRIM associated immunosuppression has been associated with a decrease in the helper:suppressor T-lymphocyte ratio, a decrease in natural killer cell function, defective antigen presentation and suppression of lymphocyte blastogenesis. Since WBC's are assumed to play a pivotal role in TRIM, it has been suggested that leukodepleted blood may have less immunomodulating properties and hence reduce the complications associated with the transfusion of non-leukodepleted blood. Hebert and colleagues reported a retrospective before-and-after cohort study conducted from August 1998 to August 2000 in 23 hospitals in Canada, enrolling 14,786 patients who received RBC transfusion following cardiac surgery or repair of hip fracture [21]. A total of 6,982 patients were enrolled during the control period and 7,804 patients were enrolled following prestorage leukoreduction. In this study the adjusted odds of death following leukoreduction were reduced (OR 0.87; CI 0.75–0.99) but serious nosocomial infections did not decrease (OR 0.97; CI 0.87–1.09). Furthermore, the frequency of febrile non-hemolytic transfusion reactions (FNHTR) decreased significantly (OR 0.86; CI 0.79–0.94) as did antibiotic use (OR 0.90; CI 0.82–0.99). While the risk of nosocomial infections were not reduced in the study by Hebert et al., a meta-analysis investigating the use of leukodepleted RBC transfusions in surgical patients demonstrated a significant reduction of postoperative infections (OR 0.522; CI 0.33–0.82, p=0.005) [22].

"Age" of Transfused Red Blood Cells

Transfused RBC's are stored refrigerated in a preservative solution. Saline-adenine-glucose-mannitol (SAG-M) is the most commonly used preservative solution and enables refrigerated storage of RBCs for up to 42 days following collection. This "shelf-life" is based on criteria set by the Food and Drug Administration (FDA), which requires that 75 % of transfused RBCs must be recoverable in the peripheral blood circulation 24 h after transfusion [23]. The reported mean storage duration of blood in the US is 18 days [2]. However this varies widely, with larger tertiary/quaternary hospitals generally transfusing older blood than smaller community hospitals. The mean age of blood transfused in ICU patients varies from about 16 to 24 days with "younger" blood being transfused in European as compared to US ICUs [6, 7]. Differences in blood banking protocols may explain this finding.

During refrigerated storage of RBC units, the RBCs undergo numerous physico-chemical changes, collectively referred to as the RBC storage lesion, which affects the quality, function and *in vivo* survival of the transfused RBCs [24, 25]. Many of these changes are the consequence of oxidative stress, leading to the generation of reactive oxygen species, altered proteins and lipids, loss of cell membrane and cell constituents forming microparticles and changes to the RBC cytoskeleton resulting in alterations in the shape and deformability of the RBC. With storage the RBC loses its biconcave shape, become more spherical and spiculated. The physical changes that occur to stored RBCs appear to be similar to those that occur to diseased RBCs (such as in malaria, sickle cell disease, thalassemia). Loss of RBC membrane results in the formation of microparticles which float in the supernatant. As a result of ongoing glycolytic metabolism, lactic acid and protons accumulate in the storage solution. Furthermore, stored white cells become activated resulting in the release of cytokine and other inflammatory mediators.

RBC Storage Lesion [25]

RBC changes

- Acidosis, decreased pH
- Slowed metabolism, decreased ATP
- Decreased 2,3 DPG, decreased O2 off-loading
- Shape change, cytoskeletal damage, band 3 denaturation
- Loss of cation pumping
- Oxidative damage, increased lipid peroxidation
- Loss of cell membrane (shedding of microparticles)
- Cell shrinkage, decreased deformability
- Loss of cell membrane phospholipid, cell asymmetry
- RBC lysis

Accumulation in the supernatant

- Acidotic, decreased pH, increased lactate
- Increased K+
- Increased free hemoglobin
- Oxidized protein and lipids
- Increased RBC microparticles
- Cell debris
- Bioactive mediators

Storage of RBC's under standard blood banking conditions results in the accumulation of cell-free and microparticle-encapsulated hemoglobin. The concentration of cell-free hemoglobin increases linearly with increasing storage time [26]. Cell-free hemoglobin is cytotoxic. The cytotoxic effect of free heme is related to its pro-oxidant activity driven by the divalent Fe atom contained within its protoporphyrin IX ring, which promotes the production of free radicals [27]. Free heme has been demonstrated to play a critical role in the pathogenesis of sepsis [28]. The pro-inflammatory cytokines released following exposure to a pathogen act synergistically with free heme to promote oxidative injury [28]. In addition, free hemoglobin binds with nitric oxide (NO) leading to endothelial dysfunction and contributing to the intravascular thrombosis, vasoconstriction, and leukocyte adhesion which occurs in the septic patient [26]. The pathogenetic importance of free heme in patients sepsis is supported by an observational study reported by Janz and colleagues who demonstrated a significant increase in the mortality of septic patients with increasing concentration of cell-free hemoglobin [29]. Heme oxygenase-1 (HO-1) is the rate-limiting enzyme in the breakdown of heme into equimolar amounts of biliverdin, iron and carbon monoxide. HO-1 has a protective effect in severe sepsis and it is likely that genetic polymorphisms of this enzyme play a role in determining the severity of the septic response [27, 28].

Oxidation of cell-free hemoglobin releases free iron. The most recent theory to explain the increased risk of infectious complications following blood transfusion and the interaction with the duration of storage relates to an increased concentration of circulating non-transferrin-bound iron, which promotes proliferation of pathogenic bacteria [30, 31]. In mouse models, transfusion of RBCs stored for longer durations was followed by brisk extravascular clearance of cells damaged during storage by macrophages in the spleen and liver [31]. The iron liberated by phagocytic digestion of these RBCs rapidly entered the systemic circulation in amounts that exceeded the transport capacity of plasma transferrin, increasing the concentration of circulating non-transferrin-bound iron. A study conducted in healthy volunteers reported the presence of higher extravascular hemolysis after older RBC transfusion (storage of 40–42 days) compared with fresh blood (storage of 3–7 days) [32]. In this study transferrin saturation and non-transferrin-bound iron increased significantly after transfusion of the old blood. The increased concentrations of non-transferrin-bound iron correlated with enhanced proliferation in vitro of a pathogenic strain of *Escherichia coli*.

A large range of adverse effects related to RBC storage have been reported in patients when RBC's stored for 2–4 weeks are transfused. These include increased

mortality, nosocomial infections, multiple organ failure, renal failure, deep vein thrombosis, and an increase in ICU and hospital length of stay and duration of mechanical ventilation [33]. However, the clinical importance of the storage lesions is controversial as all of the studies demonstrating an association between storage time and adverse outcomes are observational studies many of which are small studies [33]. Furthermore, a number of studies have been unable to find an association between adverse clinical outcomes and the duration of storage [25, 33]. Those studies that have shown an increased risk of complication with "old" blood suggest that the increased risk of complications occurs with blood stored for longer than 14 days [10, 33, 34]. To complicate this issue further, Phelan et al. demonstrated that the deleterious effects of aging on banked blood are ameliorated by pre-storage leuko-reduction [35, 36].

Currently a number of RCT's are being conducted which should help resolve this controversial issue. The Canadian ABLE study (Age of Blood Evaluation trial) is planned to enroll a total of 2,510 ICU patients in Canada, France, and the United Kingdom who will be randomized to standard transfusion practice or receive fresh blood (7 days or less) [37]. TRANSFUSE (clintrial.gov NCT01638416) is a large (5,000 patients) pivotal, multicenter, randomized, controlled trial in critically ill patients to determine whether, compared with standard care, transfusion of the freshest available RBC decreases patient mortality. The Red Cell Storage Duration Study (RECESS) is a similar study in patients undergoing cardiac surgery (clintrial. govNCT00991341), while the *Age of Blood in Children in Pediatric Intensive Care Units* (ABC PICU) study (clintrial.gov NCT01977547) is investigating the effect of fresh versus aged blood in pediatric ICU patients.

The most important complications associated with the transfusion of packed red cells are reviewed below (briefly).

Increased Risk of Postoperative and Nosocomial Infections

Starting in the mid-1980s, a dose–response relationship has been reported between the quantity of RBC's transfused and infections in various settings. Multiple observational studies have demonstrated that blood transfusion is associated with an increased risk of postoperative and nosocomial infections, increased length of hospital stay and increased mortality. While sicker patients receive more blood transfusions, multivariate analysis has consistently demonstrated that blood transfusions are independent predictors of infectious complications, morbidity and mortality. We performed a meta-analysis of 45 cohort studies that assessed the effect of RBC transfusion on patient outcomes [15]. These studies included postoperative, cardiac and ICU patients. Twenty-two studies examined the association between RBC transfusion and nosocomial infection; in all these studies blood transfusion was an independent risk factor for infection. The pooled odds ratio for developing an infectious complication was 1.8 (95 % CI; 1.5–2.2). Hill and colleagues performed a meta-analysis of studies investigating the risk of postoperative infections in patients receiving a blood transfusion [38]. In this study, the odds ratio ranged from 1.43 to

15.15, with a common odds ratio of 3.45. A more recent meta-analysis by Rohde et al. demonstrated that in hospitalized patients a liberal transfusion strategy (as compared to a restrictive strategy) was associated with an increased risk of health care associated infections [39]. It is important to note that leukodepletion has reduced but not eliminated the risk of infections complications following a blood transfusion. A metaanalysis by Blumberg et al. reported that leukoreduced transfusions reduced the odds of a postoperative infection by approximately 50 % (OR 0.522; CI 0.332–0.821; p = 0.005) [22]. In a large prospective study which included 5,158 adult patients undergoing cardiac surgery at 10 centers in the United States and Canada, Horvath and colleagues demonstrated **a** dose-related association between the quantity of RBCs transfused (all leukocyte-reduced) and risk of infection, with the risk increasing by an average of 29 % with each RBC unit transfused [40]. Similarly in ICU patients, Juffermans and colleagues have demonstrated that transfusion of leukodepleted blood increases the risk of secondary infections [41, 42]. In this study patients who received older blood had an increased risk of infections [42]. These studies provide overwhelming evidence that RBC transfusions increase the risk of postoperative and nosocomial infections; this risk is reduced but not eliminated by the transfusion of leukodepleted blood.

Febrile Non-hemolytic Transfusion Reactions (FNHTR)

A FNHTR is defined, arbitrarily, as a temperature increase of 1 °C (1.8 °F) or more associated with a RBC transfusion in the absence of any other likely causes for fever [43]. This reaction may occur either during or up to 1–2 h following the transfusion. Additional features include increases in respiratory rate, changes in blood pressure, anxiety and, more unusually, nausea or vomiting. FNHTRs are the most commonly encountered transfusion reaction occurring in approximately 0.5–2.0 % of units transfused and are more likely to occur following transfusion of platelets than RBCs. FNHTRs and believed to be due to leucocyte activation, either donor or receipt with the release of cytokines (similar mechanism to acute TRALI). Leucocyte reduction decreases the incidence of FNHTRs with prestorage leucocyte reduction being more effective than post-storage leucocyte reduction. Fever following a transfusion is attributed to FNHTR when other potential life-threatening transfusion reactions, such as acute homolytic transfusion reaction, bacterial contamination or TRALI are excluded. In patients with suspected FNHTR the transfusion should be immediately discontinued. The remainder of the transfused unit and a post-transfusion blood sample from the patient should be sent to the laboratory for further investigation. FNHTRs are typically benign, and usually resolve completely within 1–2 h after the transfusion is discontinued. Antipyretics may be administered to shorten the duration of the fever and provide analgesia. About 10–15 % of patients who experience an FNHTR may have a similar reaction in the future transfusion [43]. Administration of antipyretics (acetaminophen) 30–60 min before starting transfusion is often recommended for a patient who has had two or more FNHTRs, although there is little data to support this approach.

Transfusion Related Acute Lung Injury (TRALI)

TRALI is a serious transfusion adverse reaction characterized by the acute onset of non-cardiogenic pulmonary edema following transfusion of blood products. Although all blood components have been implicated, TRALI is more commonly associated with plasma-containing products (e.g., FFP and aphaeresis platelets), which account for the majority (50–63 %) of TRALI fatalities. TRALI is characterized by the abrupt onset of respiratory failure within 6 h following the transfusion of a blood product. While TRALLI is usually mild and resolves within hours it is the commonest cause of death following the transfusion of a blood product. It is likely that TRALI is underdiagnosed with the features of respiratory compromise frequently being ascribed to circulatory overload (TACO). TRALI is usually caused by donor anti-leukocyte antibodies. A single unit of packed cells or blood component product (FFP and platelets) is usually implicated in initiating this syndrome. It has, however, recently been recognized that the transfusion of blood products in critically ill or injured patients increases the risk for the development of acute lung injury (ALI) 6–72 h after the transfusion. This "Delayed TRALI Syndrome" is common, occurring in up to 25 % of critically ill patients receiving a blood transfusion, and is associated with a mortality of up to 40 % [44]. While the delayed TRALI syndrome can develop after the transfusion of a single unit, the risk increases as the number of transfused blood products increase. The management of both the classic and delayed TRALI syndromes is supportive.

Transfusion Associated Circulatory Overload (TACO)

TACO is defined as cardiogenic pulmonary edema that occurs during or immediately following a blood transfusion. It is believed to occur due to rapid intravascular volume expansion in the setting of diminished cardiac reserve (systolic or diastolic heart failure). It may be quite difficult to distinguish TACO from TRALI; however patients with TACO are likely to have abnormal LV function on echocardiography.

Transfusion-Associated Thrombosis

The transfusion of stored RBC increases the risk of thrombotic complications. A number of mechanisms have been postulated to explain this finding [45]. The microparticles shed from the RBC membrane contain high concentrations of phosphatidyl-l-serine, a potent promoter of factor VIIa activation and thrombin generation [46]. Plasminogen activator inhibitor 1 (PAI-1) accumulates in stored blood. The transfusion of blood products has been associated with the release of CD40 ligand from platelets. CD40L binding to vascular endothelial cells stimulates the expression of metalloproteinases, matrix-degrading enzymes implicated in plaque rupture and thrombosis. RBC transfusions in patients with cancer, traumatic injuries and subarachnoid hemorrhage have been reported to have an increased risk of

venous thromboembolism and arterial thromboses [47–49]. Increasing storage time (presumably with an increased released of bioactive lipids) appears to increase the pro-thrombotic properties of transfused blood [48].

Decreased Survival and Tumor Recurrence Following Surgery

As blood transfusions may result in immune tolerance and interfere with immune surveillance it has been suggested that perioperative blood transfusions may increase the likelihood of tumor recurrence. Evidence for a possible deleterious effect of allogenic blood transfusion has been reported in the context of tumors of the colon, rectum, breast, head and neck, lung, prostrate, stomach, kidney, cervix and vulva [50]. In a prospective study by Nosotti and colleagues in patients with stage I lung cancer undergoing lobectomy, blood transfusion resulted in decreased disease-free and overall survival [51]. A meta-analysis of randomized controlled studies of patients undergoing curative resection of colorectal cancer by the Cochrane group reported a pooled odds ratio of cancer recurrence of 1.42 (95 % CI, 1.20–1.67) associated with blood transfusion [52]. More recently Ng and colleagues demonstrated that transfusion of leukodepleted blood (as compared to no transfusion) was associated with a worse disease-free and overall survival in patients with resected stage I non-small cell lung cancer [53].

Blood transfusion should be considered as an organ transplant. The need for transfusion should be carefully evaluated, avoided when possible and considered only as a last-resort life-saving measure.

Tolerance to Anemia

In health, the amount of oxygen delivered to the whole body exceeds resting oxygen requirements almost fourfold. An isolated decrease in hemoglobin concentration to 10 g/dL with all other parameters remaining constant will result in an oxygen delivery that remains approximately twice that of the resting oxygen consumption. Humans have a remarkable ability to adapt to anemia by increasing cardiac output (in the absence of volume depletion), increasing microcirculatory density, as well as by increasing red cell synthesis of 2,3-DPG with a resultant rightward shift of the oxyhemoglobin dissociation curve (aids oxygen unloading) and by increasing oxygen extraction. Healthy volunteers can tolerate isovolemic hemodilution down to hemoglobin concentration of 4.5 g/dL without apparent harmful effects [54]. However, due to the high extraction ratio of oxygen in the coronary circulation, coronary blood flow appears to be the major factor which limits the tolerance of low hemoglobin concentrations. In experimental animal models of coronary stenosis, depressed cardiac function occurs at hemoglobin concentrations between 7 and 10 g/L [55, 56].

Extensive experience in patients who decline blood for religious reason, as well as in patients with chronic renal disease, myelodysplastic syndromes and severe autoimmune hemolytic anemias have confirmed that humans tolerate extreme anemia quite well [57, 58]. The best data comes from the Jehovah Witness literature [57]. Carson and colleagues performed a retrospective cohort study in 1,958 patients who underwent surgery and declined blood transfusions for religious reasons [59, 60]. In those patients without cardiovascular disease and with a blood loss of less than 2.0 g/dL there was no significant increase in perioperative mortality (for a baseline hemoglobin of 6–6.9 g/dL and a decline in hemoglobin of less than 2 g/dL the odds ratio (OR) for death was 1.4; 95 % CI, 0.5–4.2). However, in patients with cardiovascular disease, pre-operative anemia was associated with a significant increase in peri-operative mortality. This data confirms that humans can adapt to very low hemoglobin levels with cardiovascular disease being the major limiting factor.

Weighing the Risks and Benefits of Blood Transfusion

The benefit/harm of blood transfusion are related to a number of factors including:

- Leukodepleted versus non leukodepleted blood
- The length of storage (age of the blood)
- The number of units transfused
- The immune status of the recipient
- The baseline hemoglobin
- Presence of coronary artery disease
- Presence of ongoing bleeding
- Presence of comorbidities

So, When Should Patients' Be Transfused?

No randomized clinical trial comparing transfusion with no transfusion has been performed. However, a number of randomized clinical trials have been conducted that compared a more or less restrictive transfusion strategy using different transfusion triggers. Three randomized controlled trials which enrolled 2,364 patients evaluated a restrictive hemoglobin transfusion trigger of <7 g/dL as compared with a more liberal trigger. These studies include:

- The Canadian Critical Care Trials Group Study (TRICC) which randomized 838 adult ICU patients to a transfusion trigger of <7 or 10 g/dL [61].
- The TRIPICU study randomized 889 pediatric ICU patients to a transfusion trigger of <7 or <9.5 g/dL [62].
- Villanueva et al. randomized 921 patients with severe acute upper gastrointestinal bleeding to a transfusion trigger of <7 or <9 g/dL [63].

The pooled results from these three studies showed that a restrictive hemoglobin transfusion trigger of <7 g/dL resulted in reduced in-hospital mortality (RR 0.74; CI 0.60–0.92), total mortality (RR, 0.80; CI, 0.65–0.98), rebleeding (RR, 0.64; CI, 0.45–0.90), acute coronary syndrome (RR, 0.44; CI, 0.22–0.89), pulmonary edema (RR, 0.48; CI, 0.33–0.72), and bacterial infections (RR, 0.86; CI, 0.73–1.00), compared with a more liberal strategy [17].

Carson et al. randomized 2,016 patients >50 years of age who had undergone hip surgery and had risk factors for cardiovascular disease to a liberal transfusion strategy (trigger of 10 g/dL) or a restrictive transfusion strategy (trigger of 8 g/dL) [64]. There is no difference in morbidly or mortality between the two groups. In a pilot study, Walsh et al. randomized "older" (>55 years of age) patients requiring mechanical ventilation to a restrictive (transfusion trigger <7 g/dL) or liberal transfusion strategy (transfusion trigger <9 g/dL) [65]. Mortality at 180 days postrandomization trended toward higher rates in the liberal group (55 %) than in the restrictive group (37 %); relative risk was 0.68 (95 % CI, 0.44–1.05; $p = 0.073$).

Anemia is a well-recognized to be a poor prognostic factor in patients with congestive cardiac failure as well as acute coronary syndromes (ACS) [66, 67]. However, this does not mean that blood transfusion improves outcome. Kansagara et al. performed a meta-analysis which included 6 RCT's and 26 observational studies investing the role of blood transfusion in patients with heart disease [68]. These authors concluded that "*evidence from suggests that liberal transfusion protocols do not improve short-term mortality rates compared with less aggressive protocols* (RR 0.94; CI 0.61–1.42)." Chatterjee et al. performed a meta-analysis investigating the association between blood transfusion and outcomes in patients with acute myocardial infarction [69]. In this meta-analysis blood transfusion increased all-cause mortality (OR 2.91; CI, 2.46–3.44, p < 0.001). Multivariate meta-regression revealed that blood transfusion was associated with a higher risk for mortality independent of baseline hemoglobin level, nadir hemoglobin level, and change in hemoglobin level during the hospital stay. Blood transfusion was also significantly associated

with a higher risk for subsequent myocardial infarction (OR 2.04; CI 1.06–3.93, p=0.03). Rao and colleagues examined the potential impact of red blood cell transfusion in 24,111 patients with ACS [70]. Blood transfusion was an independent predictor of myocardial infarction and 30-day all-cause mortality (adjusted hazard ratio 3.94). Furthermore, the 30-day mortality was significantly increased when transfusions were given to patients with hematocrits of 25 % or above (compared to those with a hematocrit below 25 %). Similarly Aronson and colleagues demonstrated an increase in mortality and the composite end-point of death/recurrent MI/heart failure in patients with acute myocardial infarction who had a hemoglobin>8 g/dL and received a blood transfusion [71].

The 2012 guidelines from the *American Association of Blood Banks* (AABB) recommend adhering to a restrictive transfusion strategy (7–8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence) [72]. Furthermore these guidelines state that "*transfusion decisions should be influenced by symptoms as well as hemoglobin concentration*" (Grade: weak recommendation; low-quality evidence). The 2013 guidelines from the *American College of Physicians* recommend recommends using a restrictive blood cell transfusion strategy (trigger hemoglobin threshold of 7–8 g/dL compared with higher hemoglobin levels) in hospitalized patients with coronary heart disease (Grade: weak recommendation; low-quality evidence) [73].

Based on current evidence in patients who are not actively bleeding, RBC transfusions should be restricted to those patients with a Hb<7 g/dL. However, it is likely that many patients can tolerate a hemoglobin concentration lower 7 g/dL, suggesting that the patients' physiologic reserve, presence of coronary artery disease and other comorbidities should be taken into account when making blood transfusion decisions. Furthermore, in most instances patients should be given one unit of RBC at a time. One unit of packed RBCs should increase levels of hemoglobin by 1 g/dL and the hematocrit by 3 %.

Coagulation Disorders in the ICU

Coagulation disorders are commonly encountered in the ICU. Many conditions including sepsis, malignancy, trauma, vasculitic disorders and obstetrical accidents may give rise a coagulopathy. In addition patients may have medical conditions which predispose them to developing a coagulopathy; e.g. patients with liver disease, renal failure, lupus, leukemia, etc. Sepsis, however, is the single most common factor leading to a coagulopathy and DIC. DIC has been reported in about 10–20 % of patients with gram-negative bacteremia and 70 % of patients with septic shock. In patients with sepsis, DIC appears to be an important independent predictor of ARDS, multiple organ dysfunction syndrome and death.

A coagulopathy is best defined as the presence of an abnormal coagulation test(s). The Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH) has sug-

gested that DIC be considered "*an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, produce organ dysfunction*' [74]. DIC is characterized by the generation of *fibrin related products* (soluble fibrin monomer, fibrin degradation products, D-dimer, etc.) and is indicative of an acquired (inflammatory) or non-inflammatory disorder of the *microvasculature*.

DIC results from the systemic activation of both the clotting and fibrinolytic systems leading to the consumption of many coagulation factors and platelets. The initial activation of coagulation in sepsis is primarily dependant on activation of the extrinsic (tissue-factor dependant) pathway. DIC is generally considered to be a systemic hemorrhagic syndrome. However, this is only because hemorrhage is obvious and often impressive. Less commonly appreciated is the formidable microvascular thrombosis that occurs. Fibrin deposition in the microcirculation is a frequent, if not invariable finding in patients with DIC. This microvascular thrombosis is closely related to the development of multiple organ dysfunction syndrome and is therefore closely linked to the prognosis of patients with DIC. This microvascular damage is especially pronounced in the lungs and kidneys. In septic patients with DIC, the thrombotic (anti-fibrinolytic) pathways tend to dominate. The DIC that characterizes the early stage of traumatic shock is characteristically hemorrhagic (fibrinolytic) which then becomes thrombotic by day 2–4; this pattern has important implications with regards to resuscitation with blood and blood products [75]. A dilutional coagulopathy and DIC frequently occur in cases of massive hemorrhage regardless of their cause. Coagulation tests can be used to assess the severity of the dilutional coagulopathy and DIC as well as their evolution under the influence of therapeutic interventions. However, coagulation tests fail to predict the risk of bleeding (see below).

The "common" causes of coagulopathy/DIC in the ICU include:

- Sepsis with DIC
- Trauma
- Massive hemorrhage
- Liver disease
- Malignancy
- Obstetrical calamities
- Excessive anticoagulation

Diagnosis of DIC

- Laboratory features
  - peripheral blood smear will show fragmented red blood cells
  - prolonged PT and PTT
  - thrombocytopenia
  - decreased levels of fibrinogen
  - decreased levels of Protein C
  - decreased levels of anti-thrombin III
  - increased levels of fibrin split products and D-dimer

- Clinical features associated with bleeding
  - bleeding from venipuncture sites, mucous membranes, hematuria, GI bleeds, intra-cerebral bleeds
  - petechia, purpura, and subcutaneous hematomas
- Clinical features of end organ damage due to thrombosis
  - acute lung injury
  - proteinuria and renal insufficiency
  - hepatocellular dysfunction
  - mental state changes and neurological deficits

The treatment of DIC remains controversial. This is primarily because there are very few studies which have objectively examined various therapeutic strategies in patients with DIC. The essential therapeutic modality is to treat the triggering disease process. Patients with DIC should NOT be given FFP in order to correct abnormal coagulation tests. The administration of FFP should however be considered in patients with DIC who are actively bleeding.

Fresh Frozen Plasma

Fresh frozen plasma (FFP) contains normal levels of the stable clotting factors, albumin and immunoglobulins [76]. It contains at least 70 % of the original coagulant factor VIII and at least similar quantities of the other labile clotting factors and natural inhibitors of coagulation.

- Derived from whole blood usually, sometimes apheresis
- Frozen within 8 h of collection
- Volume: 200–250 mL
- Storage: frozen up to 1 year
- Content: "normal" levels of all coagulation factors
- Expiration: 24 h after thawing
- The recommended therapeutic dose of FFP is 10–15 mL/kg of body weight
- ABO compatibility required, crossmatching not required
- Of all the individual blood components FFP is one of the most hazardous, the major risks include:
  - TRALI
  - Allergic reactions
  - Transmission of infections
  - Fluid overload
  - Increased risk of infections
  - Hemolysis due to anti-A and anti-B

FFP is an important cause of TRALI. Khan et al. demonstrated that TRALI was more likely to develop in patients who received FFP transfusions (OR, 2.48; 95 % CI, 1.29–4.74) and platelet transfusions (OR, 3.89; 95 % CI, 1.36–11.52) than in

those who received only RBC transfusions (OR, 1.39; 95 % CI, 0.79–2.43) [77]. Watson demonstrated that FFP was an independent predictor of MODS and ALI in trauma patients [78]. In addition, similar to blood transfusion, transfusion of FFP has been associated with an increased risk of infections in ICU patients [79].

Indications for FFP [76]

- Ongoing bleeding in patients with liver disease
- Together with vitamin K and 3-factor prothrombin complex concentrate (used for severe bleeding) for reversal of prolonged INR in patients with Coumadin related bleeding
- Patients with acute disseminated intravascular coagulation (DIC) and active bleeding
- Prevention of bleeding in patients undergoing surgery or invasive procedures in whom the INR > 1.8
- Apheretic treatment of thrombotic microangiopathies (TTP)
- Hereditary angioedema due to deficiency of the inactivator of C1 esterase, in the absence of the specific plasma derivative
- Damage control resuscitation together with RBCs

Hemorrhage accounts for 40 % of deaths from trauma and is the most common cause of preventable mortality. Trauma-induced coagulopathy is multifactorial in origin and includes dilution, acidosis, hypothermia and a process known as acute traumatic coagulopathy characterized by global anticoagulation and fibrinolysis [80]. Damage control resuscitation targets acute traumatic coagulopathy with the early administration of FFP. Evidence from both civilian and military practice suggests improved outcomes with damage control resuscitation [80, 81]. While varying ratios of FFP to RBC have been proposed the optimal ratio appears to be between 1:1 and 1:2 [80, 81]. An additional theoretical benefit of FFP relates to its effect on the endothelial glycocalyx (see Chap. 9). Experimental models have demonstrated marked degradation of the endothelial glycocalyx following hemorrhagic shock [82, 83], which was restored following an infusion of FFP [83]. Resuscitation with FFP may therefore improve both coagulation as well as endothelial integrity with improved microvascular blood flow following traumatic injuries [83].

FFP Prior to Invasive Bedside Procedures or Surgery

Over four million units of FFP are transfused annually in the United States. Approximately 1/3 of all FFP is used to prepare patients with an elevated INR or PTT for a procedure [84]. Transfusion of FFP prior to an invasive procedure in patients with abnormal coagulation test results rests upon two assumptions: [85]

- that abnormal coagulation test results identify patients at increased risk of procedure-related bleeding and
- that transfusion of FFP will reduce that risk

For patients with mild to moderate abnormalities of coagulation test results, evidence to support these two assumptions is scant to non-existent. A growing body of literature documents that the INR and PTT do not predict which patients will have procedure-related bleeding and should not be used to make decisions about prophylactic preprocedure transfusions [86]. Several factors account for this lack of predictive value for bleeding. Coagulation tests such as the PT and PTT were developed primarily to identify specific coagulation deficiencies such as hemophilia. In addition, they are carried out *in vitro* (in a test tube), at room temperature, and may fail to reflect the efficacy of coagulation pathways *in vivo*, which are affected by both core temperature and the interaction with circulating cells and substances. Clinical data suggests that there is no increased risk of bleeding in patients with PT or INR values within 1.5–1.8 times the normal range. In a review of 25 studies of patients undergoing invasive procedures, Segal et al. determined that "*that there was insufficient evidence to conclude that abnormal test results predict bleeding*". Matevosyan et al. measured factors II, VII and VIII in neurosurgical patients with a prolonged INR (1.3–1.7) [87]. In this study all patients with a mildly prolonged INR had levels of coagulation facts within the hemostatic normal range. Based on this data the authors recommended that plasma not be transfused to simply correct this abnormal laboratory value.

The second assumption of preprocedure FFP transfusion is that the infused product will correct the coagulopathy. For the great majority of patients who are given such transfusions—namely, those with mild to moderate prolongation of the INR—there is very little evidence to support this assumption [85]. In fact, the evidence speaks to the contrary. Holland and Brooks reported the effect of FFP on the INR in 179 patients with a prolonged INR who were given FFP for a variety of indications [88]. For patients with INR's of 1.7 or less, infusion of FFP in typical doses used had no effect on the patient's INR. For patients with INR values greater than 2, the correction of INR was modest and incomplete. For example, even for patients with an INR = 4.0, the average correction with FFP transfusion was partial resulting in an INR = 3.0. Similar findings were reported by Abdel-Wahab et al. who noted that among 121 adult patients with a pretransfusion INR of 1.6 or less who were given 1–4 units of FFP, the posttransfusion INR corrected to within the normal range in only two patients [89]. In a population of stable trauma patients McCully demonstrated that the use of FFP did not affect coagulation factor function and that the INR did not predict bleeding [90].

The exponential shape of the INR curve implies that increasing the concentration of clotting factors by FFP transfusion will have a substantial correcting effort on the INR when the pretransfusion INR level is markedly prolonged but will have an ever-diminishing impact as the pretransfusion INR approaches the normal physiologic range [85]. This data suggests that as a general rule FFP should not be transfused prophylactically in patients with an INR < 1.8 undergoing an invasive procedure. In patients' with an INR ≥ 1.8 the risk/benefits of pre-procedure FFP should be weighed in each patient; should FFP be infused, normalization of the INR should not be attempted. FFP should not be administered prophylactically to patients with normal

coagulation tests undergoing high risk surgery or invasive diagnostic tests in an "attempt to limit bleeding".

Coagulopathy and Central Venous Catheterization

In many instances central venous catheterization is required in patients with a coagulopathy in whom correction of the coagulopathy prior to line placement is not possible. However, the risk of bleeding appears to be increased only in patients with an INR > 2.0 and a platelet count < 20×10^9 L^{-1}. Doerfler described their experience with placement of 104 central lines in 76 coagulopathic medical patients. All insertions were performed by experienced operators; none of the patients received "prophylactic" transfusions of platelets or FFP [91]. There were no serious bleeding complications, with only minor bleeding (skin) in 7 (6.5 %) patients (who had a mean platelet count of 22,000 μL^{-1}). Similarly, Mumtaz et al. reviewed their experience in 330 surgical patients with disorders of hemostasis [92]. In 88 of the 330 patients, the underlying coagulopathy was not corrected before catheter placement. In these patients, there were three bleeding complications requiring placement of a purse string suture at the catheter entry site. These authors concluded that "*central venous access procedures can be safely performed in patients with underlying disorders of hemostasis. Even patients with low platelet counts have infrequent (3 of 88) bleeding complications and these problems are easily managed.*" Fisher and colleagues reported their experience with 658 central venous cannulations in patients with liver disease and a coagulopathy (mean INR 2.4, platelet count 81,000 μL^{-1}), none who received prophylactic transfusions of either FFP or platelets [93]. These authors reported only one major bleeding complication (a hemothorax after accidental subclavian artery cannulation) with minor oozing or local hematoma in 6 % of patients. Goldfarb et al. reported their experience with 1,000 cannulations of the internal jugular vein to facilitate obtaining a transvenous liver biopsy [94]. All the patients had coagulopathies (prothrombin time activity less than 50 % and/or a platelet count less than 50,000 μL^{-1}). In 74 patients, the common carotid artery was inadvertently punctured. A clinically detectable hematoma occurred in ten patients; in one patient, the hematoma compressed the airway; this patient recovered completely after a surgical drainage. In this patient, puncture of the internal jugular vein was difficult because of a goiter, but the carotid artery apparently was not punctured. Similarly, Foster and colleagues reported on their experience with 200 cannulations in patients undergoing liver transplantation who had coagulopathies (that remained uncorrected) [95]. These authors reported no cases of bleeding complications.

This data indicates that the risk of bleeding is related to the skill of the operator and not the ability of the blood to clot. In the hands of an experienced operator the risk of bleeding may be higher in patients with a platelet count less than 20,000 μL^{-1}; in these patients a platelet transfusion should be considered (if existing venous access allows). In the hands of the inexperienced operator, the femoral site (which

is compressible) is recommended (in the coagulopathic patient). However, even in this circumstance the risks of blood product transfusion likely exceed the benefit.

Thoracentesis and Chest Tube Placement

Hemothorax and pulmonary hemorrhage are very rare complications of thoracentesis; these complications have occurred in patients with normal hemostasis. McVay et al. reported no bleeding complications in patients with a mild to moderate coagulopathy (defined as PT or PTT twice normal or a platelet count of 50,000–99,000 μL^{-1}) who underwent a thoracentesis [96].

Hibbert et al. evaluated the risk of bleeding following 1,009 ultrasound guided thoracentesis in patients with an INR > 1.5 and/or a platelet count < 50,000 μL^{-1} [97]. In this study the mean INR was 1.9, the mean platelet count was 190,000 μL^{-1} with 25 % of patients having a platelet count of <50,000 μL^{-1} and 81 % of patients having an INR > 1.6. A hemorrhagic complications occurred in 0.4 % of patients in who did not receive pre-procedure coagulation factors as compared to 1.32 % in those patients in whom attempts were made to correct the INR and/or platelet count. This data would suggest that replacement with coagulation factors may only be required when the platelet count < 20,000 μL^{-1} and/or the INR > 2.0. As chest tube placement is more "invasive" than thoracentesis a platelet count > 50,000 μL^{-1} and INR > 2 is suggested.

Paracentesis

According to the position state of the American Association for the Study of Liver Disease (AASLD) "*the practice of giving blood products (fresh frozen plasma and/or platelets) routinely before paracentesis in cirrhotic patients with coagulopathy is not data-supported. The risks and costs of prophylactic transfusions exceed the benefit*" [98]. The guideline states that "*since bleeding is sufficiently uncommon, the prophylactic use of fresh frozen plasma or platelets before paracentesis is not recommended*".

Management of Non-therapeutic INRs With or Without Bleeding (Due to Coumadin Therapy)

For most indications, an INR range of 2.0–3.0 is targeted; INR values less than 2.0 are associated with an increased risk for thromboembolism, and INR values greater than 4.0 are associated with an increase in bleeding complications. The risk for bleeding, particularly intracranial bleeding, increases markedly as the INR exceeds 4.5.

The management of patients whose INR is outside the therapeutic range is controversial because many of the various options have not been compared. The

interventions include administering vitamin K and/or infusing fresh frozen plasma, prothrombin concentrates or recombinant factor VIIa. The preferred approach is based largely on the potential risk of bleeding, the presence of active bleeding, and the level of the INR [99]. Phytonadione (vitamin K1, a form of vitamin K derived from plants) has been used in the treatment of warfarin-associated coagulopathy [100]. When oral phytonadione is administered in conjunction with temporary interruption of warfarin therapy, approximately 1.4 days are required for an INR between 6 and 10 to decline to <4.0 [100]. When administered intravenously, low doses of phytonadione produce similar reductions as oral phytonadione in the INR value at 24 h, whereas subcutaneous phytonadione appears to be less effective than low-dose oral phytonadione. The response to vitamin K administered subcutaneously is less predictable than that of oral or IV vitamin K. Dezee performed a meta-analysis of trials that used vitamin K to treat patients without major hemorrhage with an INR greater than 4.0 [101]. The primary outcome was achievement of the target INR (1.8–4.0) at 24 h after vitamin K administration. This study demonstrated equal efficacy of oral and IV vitamin K (1.0–2.5 mg) in normalizing the INR, whereas subcutaneous vitamin K was no better than placebo.

When administered at higher doses for the management of the bleeding patient, intravenously administered phytonadione works more rapidly than either oral or subcutaneous vitamin K1 [100]. Reduction of the INR begins within 2 h, and a correction to within the normal range is generally achieved within 24 h if hepatic function is normal and if a sufficiently large dose is given. To minimize the risk of anaphylactoid reactions, vitamin K1 should be mixed in a minimum of 50 mL of intravenous fluid and administered, using an infusion pump, over a minimum of 20 min [100]. High doses of vitamin K, though effective, may lower the INR more than is necessary and may lead to warfarin resistance for 1 week or more. Low doses of vitamin K are therefore recommended. A dose of 1.25 is recommended when the INR is between 4.0 and 9.0, but larger doses (i.e., 2.5–5 mg) are required to correct INRs of >9.0.

For life-threatening bleeding, immediate correction of the INR is mandatory. Although fresh frozen plasma can be given in this situation, immediate and full correction can only be achieved by the use of factor concentrates because the amount of FFP required to fully correct the INR is considerable and may take hours to infuse. Prothrombin Complex Concentrates (PCC) are recommended in these patients. PCCs do not require a cross-match, are virally inactivated, do not pose a risk of volume overload, and can be infused in 15–30 min. PCC may be classified as Three-Factor products (with adequate levels of factors II, IX, X, and low factor VII levels) and Four-Factor products (4-factor PCC), which contain adequate levels of factors II, VII, IX, and X as well as protein C and S. Hickey et al. compared the use of FFP with a 4-factor PCC in patients who required emergent reversal of Coumadin [102]. In this study the 4-factor PCC resulted in faster reversal and lower red cell transfusion requirement with fewer adverse events than FFP.

Kcentra is first non-activated 4-factor PCC available in the USA. Pabinger et al. demonstrated that Kcentra reduced the INR to less than 1.3 at 30 min in 93 % of patients who required emergent reversal [103]. Kcentra is dosed in units of factor IX (500 units factor IX per vial) as follow:

- For a pretreatment INR of 2–4, administer 25 units/kg IV, with a maximum dose of 2,500 units.
- For a pretreatment INR of 4–6, administer 35 units/kg IV, with a maximum dose of 3,500 units.
- For a pretreatment INR greater than 6, administer 50 units/kg IV, with a maximum dose 5,000 units.

OR

- Patients INR (max 8.00) × Weight in kg (max 100) × 6.25 = Number units.

ACCP Guidelines for managing elevated INR's (due to Coumadin) [99]

- INR more than therapeutic range but <5.0; no significant bleeding
  - Lower dose or omit dose; monitor INR
- INR ≥ 5.0, but <9.0; no significant bleeding
  - Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (1.25 mg po), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K (2.5–5 mg po) can be given with the expectation that a reduction of the INR will occur in 24 h.
- INR ≥ 9.0; no significant bleeding
  - Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg po) with the expectation that the INR will be reduced substantially in 24–48 h. (Grade 1B). Monitor more frequently and use additional vitamin
- Serious bleeding at any elevation of INR
  - Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion) and FFP; vitamin K can be repeated q12h
- Life-threatening bleeding
  - Hold warfarin therapy and give 4-factor PCC with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR

Platelet Transfusion

Thrombocytopenia (defined as a platelet count < 100,000 μL^{-1}) is a common problem in ICU patients and is associated with adverse outcomes. A platelet count of less than 100,000 μL^{-1} is seen in 20–50 % of ICU patients, whereas 12–15 % of patients will have a platelet count of <50,000 μL^{-1} at some point during their ICU admission [104–106]. Typically the ICU patient's platelet count decreases during the first 4 days in the ICU [107]. Regardless of the cause, thrombocytopenia is an independent predictor of ICU mortality in multivariate analysis with a relative risk of 1.9–4.2 in various studies [105]. In an observational study of 820 patients with severe community acquired pneumonia admitted to the ICU, Brogly et al. found that thrombocytopenia on admission was an independent predictor of mortality [108]. Moreau

reported that a 30 % or more decline in platelet count by the fifth ICU day was an independent predictor of death [106].

The causation of thrombocytopenia in ICU patients is often multifactorial, with sepsis being the most important cause. Thrombocytopenia is an early sign of sepsis and may occur in the absence of other features of DIC. Dilutional thrombocytopenia due to blood and fluid replacement is the second most common cause of thrombocytopenia in the ICU. Other causes include:

- Consumptive coagulopathy (DIC) due to liver failure, HELP syndrome, abruption placentae
- Microangiopathic hemolytic anemia; i.e. Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS)
- Immune thrombocytopenias
  - idiopathic (ITP)
  - heparin (see below)
  - allo-antibodies
  - collagen vascular diseases
  - malignancy
  - viral
  - drug induced
- Myelosuppressive chemotherapeutic agents
- Drugs are commonly implicated in the etiology of thrombocytopenia. Almost any drug can cause a thrombocytopenia. The commonly implicated drugs include:

  Antimicrobials

  - linezolid
  - vancomycin
  - fluoroquinolones
  - amphotericin
  - tetracyclines
  - sulfonamides
  - penicillins
  - chloramphenicol
  - cephalosporins

  Anticonvulsants

  - phenytoin (Dilantin)
  - carbamazepine

  Diuretics

  - furosemide
  - thiazides
  - ethacrynic acid

Others

- ○ alcohol
- ○ phenylbutazone
- ○ aspirin
- ○ gold salts
- ○ colchicine
- ○ chlorpromazine
- ○ chlordiazepoxide
- ○ H2 blockers

Up to 25 % of acutely ill patients develop drug-induced thrombocytopenia (DIT) [109]. The mechanism of DIT is decreased platelet production from bone marrow suppression, increased platelet destruction, or platelet sequestration. DIT can develop from either nonimmune or immune causes. Nonimmune-mediated DIT is the result of bone marrow suppression from agents including antineoplastics, antivirals, ethanol, thiazide diuretics, and tolbutamide, and it develops slowly over a period of several weeks. Heparin is the medication most commonly associated with DIT. A nonimmune-mediated and an immune-mediated form of thrombocytopenia occur from heparin (see HIT below). Nonimmune-mediated thrombocytopenia occurs in 10–20 % of patients receiving unfractionated heparin 1–4 days after initiation. Platelets typically do not decrease to 100×10^9 L^{-1}. Linezolid is the antimicrobial most likely to cause thrombocytopenia. The mechanism of thrombocytopenia is not fully understood, although potential mechanisms include direct myelosuppression and immune mediated platelet destruction. Vancomycin and fluoroquinolones may be under-recognized as a cause of thrombocytopenia [109].

A large percentage of thrombocytopenic patients in the ICU receive a platelet transfusion. Many of these transfusions are administered outside of published guidelines [110]. This is important as platelet transfusions are not benign, being associated with many of the same complications as FFP, including TRALI, immune sensitization, etc. Platelets are obtained by two different methods; i.e., preparing platelet concentrates from donated units of whole blood, and by platelet apheresis procedures. The "composition" of pheresed (SDP) as well as single and pooled whole blood derived platelets (WBDP) as listed in Table 38.2.

Platelet transfusion may be indicated to prevent hemorrhage in patients with thrombocytopenia or platelet function defects (see Table 38.3). Contraindications to platelet transfusion include thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia. Transfusion of platelets in these conditions can result in further thrombosis [76, 111]. One unit of apheresis platelets should increase the platelet count in adults by 30,000–60,000 μL^{-1}. The platelet count should be measured within an hour of transfusion. Both hemorrhage and the underlying conditions that cause bleeding may increase platelet consumption and appreciably shorten platelet survival. Most ICU patients respond poorly to platelet transfusion.

Table 38.2 Platelet product contents

	Pheresis (SDP)	WBDPs (single unit)	WBDP pool (5 units)
Platelets Av	$\sim 4.2 \times 10^{11}$	$\sim 7\text{--}9 \times 10^{10}$	$\sim 4 \times 10^{11}$
Leukocytes	$10^5\text{--}10^7$	$\sim 8 \times 10^7$	$\sim 4 \times 10^8$
RBC	Rare	<1 mL	<5 mL
Volume (mL)	200–300	45–60	~300
Matching potential	Yes	Yes	No
Shelf life	5 days	5 days	5 days

Table 38.3 Indications of platelet transfusion

Prophylactic transfusion indication	Platelet count $x \times 10^9\ L^{-1}$
Major surgery or invasive procedure, no bleeding	≤ 50
Epidural anesthesia, gastroscopy and biopsy, transbronchial biopsy, liver biopsy	≤ 50
Ocular surgery or neurosurgery, no bleeding	≤ 100
Lumbar puncture	<20
Surgery active bleeding	<50
Stable, non-bleeding	<10
Stable non-bleeding and minor procedure	<20

Salman et al. studied 90 ICU patients who received a platelet transfusion; the mean increase in platelet count was 22,600 μL^{-1} with 64 % having a poor response (defined as an increase of <30,000 μL^{-1} after 6 units WBDP [104].

Spontaneous bleeding through intact endothelium does not occur unless the platelet count is less than 5,000 μL^{-1} [76, 111]. Previously, a platelet count of 20,000 μL^{-1} was considered to be an indication for a prophylactic platelet transfusion. However, four randomized prospective transfusion trials comparing prophylactic platelet transfusion triggers of 10,000 μL^{-1} versus 20,000 μL^{-1} showed no differences in hemorrhagic risks [111].

Elderly patients are frequently prescribed anti-platelet drugs; intracerebral hemorrhage is not an uncommon complication in these patients. Platelet transfusion has therefore been considered in patients taking an anti-platelet drug who suffer an intracerebral bleed. While no RCT has been performed data from observational studies suggest the platelet transfusions do not improve outcome [112]. There is currently an ongoing study known as the Platelet Transfusion in Cerebral Hemorrhage trial, which aims to answer this question in the setting of spontaneous intracerebral hemorrhage [113]. This is a prospective, randomized, multicenter study, which will examine the effect of platelet transfusion within 6 h compared with standard care.

Heparin Associated Thrombocytopenia

Recognition of heparin-induced thrombocytopenia (HIT) and HIT with thrombosis (HITT) is of particular importance given its paradoxical association with thrombosis. HIT/HITT is an immune-mediated disorder that is triggered by exposure to any form of heparin; it is also known as type II HIT, to distinguish it from the non-immune-mediated, mild thrombocytopenia associated with heparin termed type I HIT. Type II HIT is caused by the generation of heparin-induced, platelet activating immunoglobulin G (IgG) antibodies that recognize heparin-platelet factor 4 complexes [114]. The resulting platelet activation and thrombin generation lead to a significant risk of both arterial and venous thrombosis. Depending on the patient population studied, the risk of thrombosis has ranged from 29 to 89 %. Even after cessation of heparin therapy, the threat of thrombosis persists. In one study, the 30-day risk of thrombosis after the diagnosis of HIT was 53 % [115]. However, only a small proportion of patients who form HIT antibodies (seroconversion) will develop thrombocytopenia, and a smaller proportion will develop HIT-associated thrombosis.

The incidence of HIT varies depending on the patient population studied and the type of heparin preparation used. Patients undergoing cardiac or orthopedic surgery are among those at highest risk of developing HIT. HIT is less common in medical patients, with studies suggesting a frequency of 1 % or less [114]. Women have approximately twice the risk of developing HIT as men. Patients receiving unfractionated heparin (UFH) are at increased risk of HIT compared with those given the low molecular weight heparin (LMWH) preparations. Diagnosis of HIT requires consideration of both clinical and serologic findings. Because nonpathogenic heparin-platelet factor 4 antibodies occur commonly in patients treated with heparin, a positive test for HIT antibodies is not sufficient to make the diagnosis. Diagnostic specificity can be increased by use of a sensitive washed platelet activation assay; a positive platelet activation assay is much more specific for clinical HIT than a positive platelet factor 4-dependent immunoassay. However, given the risk of thrombosis in patients with HIT, appropriate therapy should not be withheld while awaiting the results of serologic testing. HIT should be suspected in patients who develop thrombocytopenia or experience a relative drop in platelet count of >50 %, typically occurring 4–10 days after initiation of heparin therapy. Thrombocytopenia may occur much more rapidly after exposure to heparin, however, in patients who have received heparin within the previous 100 days. New or recurrent venous or arterial thromboses in patients who are receiving, or have recently received, a heparin product should also raise suspicion for HIT. It should be appreciated that in about 25 % of HIT patients, a thrombotic event during heparin treatment precedes the subsequent HIT-associated platelet count fall [114].

Only a subset of anti-PF4/heparin antibodies activate platelets. There is a correlation between the degree of reactivity in the EIA, expressed in optical density (OD) units, and the presence of PF4/heparin antibodies. Thus, the greater the magnitude

Table 38.4 4T score to determine the likelihood of HIT

	Score = 2	Score = 1	Score = 0
Thrombocytopenia	>50 % fall and nadir > 20 AND no surgery within 3 days	>50 % fall BUT surgery within 3 days or 30–50 % platelet fall or nadir 10–19	<30 % platelet fall or nadir < 10
Timing	5–10 days after start of heparin or fall within 1 day of start heparin and exposure to heparin within past 5–13 days	Platelet fall within 1 day of heparin AND exposure to heparin in past 31–100 days or platelet fall after day 10	Platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis	Confirmed new thrombosis, skin necrosis at injection site, adrenal hemorrhage	Recurrent venous thrombosis in patient receiving therapeutic anticoagulation or suspected thrombosis (awaiting confirmation)	Thrombosis not suspected
OTher causes	No alternative cause for platelet fall evident	Possible other cause	Probable other cause

Score 0–3 low risk, 4–5 intermediate risk, score 6–8 high risk

of a positive EIA test result, the greater the likelihood that the patient has HIT. Functional assays, such as the serotonin release assay (SRA) and heparin induced platelet activation (HIPA) are sensitive and specific for HIT because they only detect antibodies that are capable of activating platelets. HIT is recognized as a clinicopathologic syndrome because diagnosis is based on the combination of a compatible clinical picture and the presence of platelet-activating anti-PF4 antibodies [116]. The 4Ts clinical prediction rule has been developed as an aid in the diagnosis of HIT (see Table 38.4) [116]. Patients with a low 4Ts score have a very low probability of HIT (0–3 %), however, many patients (24–61 %) with a high 4Ts score prove not to have HIT [116, 117]. This suggests that clinical assessment plays an essential role in the diagnosis of HIT.

If HIT is suspected, all heparin products must immediately be discontinued. Given the high risk of thrombosis with HIT it is currently recommended that an alternate, non-heparin anticoagulant replace heparin in patients strongly suspected of having HIT [114]. The ACCP guidelines recommend that following agents for the treatment of HIT [116]:

- argatroban or lepirudin in patients who have normal renal function
- argatroban in patients with renal insufficiency
- bivalirudin in patients who require urgent cardiac surgery

For patients receiving lepirudin, the initial lepirudin infusion rate should be no higher than 0.10 mg/kg/h. The usual starting dose of argatroban is 2.0 μg/kg/min with dosage adjustment according to the PTT. In patients with heart failure, multiple organ system failure, or severe anasarca or who are postcardiac surgery, an initial infusion at a rate between 0.5 and 1.2 μg/kg/min is recommended [114]. In patients

with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery, the ACCP guidelines suggest the use of heparin (short-term use only) over non-heparin anticoagulants. In patients with a history of HIT in whom heparin antibodies are still present who require cardiac surgery, the ACCP guidelines suggest the use of non-heparin anticoagulants over heparin or LMWH [116]. In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, the ACCP guidelines recommend the use of fondaparinux at full therapeutic doses until transition to Coumadin can be achieved. In patients with HIT and severe thrombocytopenia, platelet transfusions should only be given for bleeding or during the performance of an invasive procedure with a high risk of bleeding [116].

Coumadin should not be started before the platelet count has increased above 150,000 μL^{-1}. Low dose Coumadin is recommended (5 mg/day) with the non-heparin anticoagulant being continued until the platelet count has reached a stable plateau, the INR has reached the intended target range, and after a minimum overlap of at least 5 days between the non-heparin anticoagulant and Coumadin. Because thrombocytopenia is common in ICU patients and because these patients are invariably receiving heparin the possibility of HIT is frequently entertained. It is important to consider HIT in thrombocytopenia patients as the consequences (to the patient and physician) are devastating should the diagnosis be missed. Consequently, these patients usually undergo an expensive and often frustrating diagnostic workup. This scenario is best avoided by minimizing the use of unfractionated heparin (UH), particularly in high risk patient groups. As the risk of HIT is lower with LMWH and essentially zero with fondaparinux, these agents are useful alternatives to UH (in patients with normal renal function).

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP) usually refers to the disorder of thrombocytopenia, hemolysis with schistocytes on blood smears, renal dysfunction and neurologic abnormalities, such as headache, confusion, focal deficits, seizures, or coma [118–120]. These manifestations are due to widespread microvascular thrombosis involving the capillaries and arterioles of the brain and other organs. Thrombocytopenia results from consumption of platelets, whereas erythrocyte fragmentation and hemolysis may be due to mechanical injury as the red cells encounter the intravascular thrombi or abnormally high levels of shear stress. Typically, TTP affects previously healthy adolescents or adults and almost invariably follows a rapid course of deterioration and death unless plasma infusion or exchange therapy is instituted immediately. A similar disorder occurs in children, the hemolytic-uremic syndrome (HUS). Childhood HUS, typically preceded by abdominal pain and diarrhea is recognized as a complication of infection caused by bacteria that produce Shiga toxins, such as Escherichia coli O157:H7. Currently, about 90 % of children with typical HUS survive with supportive care, without plasma exchange treatment.

Common clinical and laboratory features of TTP

- Thrombocytopenia
- Microangiopathic hemolytic anemia
- Neurologic abnormality or complaint
- Renal abnormalities
- Proteinuria and microscopic hematuria
- Increased BUN and creatinine
- Temperature > 38.3 °C
- Microthrombi on tissue biopsy

Exclusion

- Evidence of intravascular coagulation
- Evidence of underlying condition associated with or producing microangiopathic syndrome
- Positive antinuclear antibody or anti-DNA antibody
- Oliguria or anuria

The pathophysiological hallmarks of acute TTP are von Willebrand factor (VWF)—platelet-rich thrombi occluding the microvasculature. The VWF-platelet thrombi are thought to be the consequence of insufficient processing of newly secreted, extremely adhesive and ultra large VWF multimers. In the majority of patients, this insufficient processing of ultra large VWF multimers is the result of a severe deficiency of the VWF-cleaving protease, now denoted as ADAMTS13 [118–120]. ADAMTS13 activity levels are less than 10 % of normal control in patients who have acute TTP. TTP is considered an autoimmune disease, with ADAMTS13-binding IgG is detectable in 97–100 % of cases.

Platelet transfusion should be avoided because bleeding complications are uncommon in TTP, and marked deterioration in neurologic status has been reported in association with platelet transfusions. In acute bouts of acquired TTP, the treatment of choice is daily plasma exchange with replacement of plasma. Plasma exchange should be initiated immediately once a diagnosis of acute TTP is seriously considered or has been established, as deferral in starting treatment is associated with increased numbers of treatment failure and adverse outcome [121]. In case plasma exchange is not available, patients should be treated with plasma infusions until their referral to a center where plasma exchange can be performed. The efficacy of plasma exchange therapy is believed to result from replenishment of the missing ADAMTS13. Although it also may remove the inhibitors, this process is not very effective and by itself is insufficient for therapeutic responses.

Plasma exchange treatment is frequently supplemented with immunosuppressive drugs. Although controlled trials are lacking, the finding that in the majority of patients, idiopathic acquired TTP is an autoimmune disorder with circulating inhibitory anti-ADAMTS13 autoantibodies leading to severe ADAMTS13 deficiency supports the potential efficacy of these drugs. Methylprednisolone is the most commonly used drug. However, the combination of plasma exchange and cyclosporine is an alternative with apparent success [122]. Rituximab, a chimeric monoclonal anti-CD20, has been used with presumed benefits in patients with protracted TTP.

Cryprecipitate

Cryoprecipitate is prepared by thawing fresh frozen plasma and collecting the precipitate. Cryoprecipitate contains high concentrations of factor VIII and fibrinogen [123]. Cryoprecipitate is used in cases of hypofibrinogenemia, which most often occurs in the setting of massive hemorrhage or consumptive coagulopathy. Each unit will raise the fibrinogen level by 5–10 mg/dL, with the goal of maintaining a fibrinogen level of at least 100 mg/dL [123]. The usual dose in adults is 10 units of pooled cryoprecipitate.

References

1. National Blood Data Resource Center. Comprehensive report on blood collection and transfusion in the United States. http://www.aabb.org/Content/Programs_and_Services/Data_Center/NBCUS/. 2001. Acessed 15 May 2007.
2. Whitaker B. Report of the United Staes Department of Health and Human Services: the 2009 National Blood Collection and Ulitization Survery Report. Washington, DC: United States Department of Health and Human Services, Office of the Assistant Secretary for Health; 2011.
3. Wells AW, Mounter PJ, Chapman CE, et al. Where does blood go? Prospective observational study of red cell transfusion in north England. Br Med J. 2002;325:803–6.
4. Hogshire L, Carson JL. Red blood cell transfusion: what is the evidence when to transfuse? Curr Opin Hematol. 2013;20:546–51.
5. Adams RC, Lundy JS. Anesthesia in cases of poor surgical risk: some suggestions for decreasing risk. Surg Gynecol Obstet. 1941;71:1011–4.
6. Corwin HL, Gettinger A, Pearl RG, et al. The CRIT study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. Crit Care Med. 2004;32:39–52.
7. Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. JAMA. 2002;288:1499–507.
8. van Woerkens EC, Trouwborst A, van Lanschot JJ. Profound hemodilution: what is the critical level of hemodilution at which oxygen delivery-dependent oxygen consumption starts in an anesthetized human? Anesth Analg. 1992;75:818–21.
9. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. JAMA. 1993;270:1724–30.
10. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. JAMA. 1993;269:3024–9.
11. Conrad SA, Dietrich KA, Hebert CA, et al. Effect of red cell transfusion on oxygen consumption following fluid resuscitation in septic shock. Circ Shock. 1990;31:419–29.
12. Creteur J, Neves AP, Vincent JL. Near-infrared spectroscopy technique to evaluate the effects of red blood cell transfusion on tissue oxygenation. Crit Care. 2009;13 Suppl 5:S11.
13. Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. JAMA. 2003;289:959–62.
14. Raghavan M, Marik PE. Anemia, allogenic blood transfusion, and immunomodulation in the critically ill. Chest. 2005;127:295–307.
15. Marik PE, Corwin HL. Efficacy of RBC transfusion in the critically ill: a systematic review of the literature. Crit Care Med. 2008;36:2667–74.
16. Marik PE. The hazards of blood transfusion. Br J Hosp Med. 2009;70:12–5.

17. Salpeter SR, Buckley JS, Chatterjee S. Impact of more restrictive blood transfusion strategies on clinical outcomes: a meta-analysis and systematic review. Am J Med. 2014;127:124–31.

18. Opelz G, Sengar DP, Mickey MR, et al. Effect of blood transfusions on subsequent kidney transplants. Transplant Proc. 1973;5:253–9.

19. Williams KA, Ting A, French ME, et al. Peroperative blood-transfusion improve cadaveric renal-allograft survival in non-transfused recipients. A prospective controlled clinical trial. Lancet. 1980;1:1104–6.

20. Lagaaij EL, Ruigrok MB, van Rood JJ, et al. Blood transfusion induced changes in cell-mediated lympholysis: to immunize or not to immunize. J Immunol. 1991;147:3348–52.

21. Hebert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. JAMA. 2003;289:1941–9.

22. Blumberg N, Zhao H, Wang H, et al. The intention-to-treat principle in clinical trials and meta-analyses of leukoreduced blood transfusions in surgical patients. Transfusion. 2007;47:573–81.

23. Roback JD, Combs MR, Hillyer CD. AABB Technical manual. 16th ed. Bethesda: American Association of Blood Banks; 2008.

24. Tinmouth A, Fergusson D, Yee IC, et al. Clinical consequences of red cell storage in the critically ill. Transfusion. 2006;46:2014–27.

25. Zimrin AB, Hess JR. Current issues relating to the transfusion of stored red blood cells. Vox Sang. 2009;96:93–103.

26. Donadee C, Raat NJ, Kanias T, et al. Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesions. Circulation. 2011;124:465–76.

27. Jeney V, Balla J, Yachie A, et al. Pro-oxidant and cytotoxic effects of circulating heme. Blood. 2002;100:879–87.

28. Larsen R, Gozzelino R, Jeney V, et al. A central role for free heme in the pathogenesis of severe sepsis. Sci Transl Med. 2010;2:51ra71.

29. Janz DR, Bastarache JA, Peterson JF, et al. Association between cell-free hemoglobin, acetaminophen and mortality in patients with sepsis: an observational study. Crit Care Med. 2013;41:784–90.

30. Ozment CP, Turi JL. Iron overload following red blood cell transfusion and its impact on disease severity. Biochim Biophys Acta. 2009;1790:694–701.

31. Hod EA, Zhang N, Sokol SA, et al. Transfusion of red blood cells after prolonged storage produces harmful effects that are mediated by iron and inflammation. Blood. 2010;115:4284–92.

32. Hod EA, Brittenham GM, Billote GB, et al. Transfusion of human volunteers with older, stored red blood cells produces extravascular hemolysis and circulating non-transferrin-bound iron. Blood. 2011;118:6675–82.

33. Aubron C, Nichol A, Cooper DJ, et al. Age of red blood cells and transfusion in critically ill patients. Ann Intensive Care. 2013;3:2.

34. Koch CG, Li L, Sessler DI, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med. 2008;358:1229–39.

35. Phelan HA, Gonzalez RP, Patel HD, et al. Prestorage leukoreduction ameliorates the effects of aging on banked blood. J Trauma. 2010;69:330–7.

36. Phelan HA, Eastman AL, Aldy K, et al. Prestorage leukoreduction abrogates the detrimental effect of aging on packed red cells transfused after trauma: a prospective cohort study. Am J Surg. 2012;203:198–204.

37. Lacroix J, Hebert P, Fergusson D, et al. The Age of Blood Evaluation (ABLE) randomized controlled trial: study design. Transfus Med Rev. 2011;25:197–205.

38. Hill GE, Frawlwy WH, Griffith KE, et al. Allogenic blood transfusion increases the risk of postoperative bacterial infetion: a meta-analysis. J Trauma. 2003;54:908–14.

39. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion. A systematic review and meta-analysis. JAMA. 2014;311:1317–26.

40. Horvath KA, Acker MA, Chang H, et al. Blood transfusion and infection after cardiac surgery. Ann Thorac Surg. 2013;95:2194–201.
41. Juffermans NP, Prins DJ, Vlaar AP, et al. Transfusion-related risk of secondary bacterial infections in sepsis patients: a retrospective cohort study. Shock. 2011;35:355–9.
42. Juffermans NP, Vlaar AP, Prins DJ, et al. The age of red blood cells is associated with bacterial infections in critically ill trauma patients. Blood Transfus. 2012;10:290–5.
43. Refaai MA, Blumberg N. The transfusion dilemma—weighing the known and newly proposed risks of blood transfusions against the uncertain benefits. Best Pract Res Clin Anesthesiol. 2013;27:17–35.
44. Marik PE, Corwin HL. Acute lung injury following blood transfusion: expanding the definition. Crit Care Med. 2008;36:3080–4.
45. Twomley KM, Rao SV, Becker RC. Proinflammatory, immunomodulating, and prothrombotic properties of anemia and red blood cell transfusions. J Thromb Thrombolysis. 2006;21:167–74.
46. Sweeney J, Kouttab N, Kurtis J. Stored red blood cell supernant facilititates thrombin generation. Transfusion. 2009;49:1569–79.
47. Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med. 2008;168:2377–81.
48. Spinella PC, Carroll CL, Staff I, et al. Duration of red cell storage is associated with inceased incidence of deep vein thrombosis and in-hospital mortality in patients with traumatic injuries. Crit Care. 2009;13:R151.
49. Kumar MA, Boland TA, Baiou M, et al. Red blood cell transfusion increases the risk of thrombotic events in patients with subarachnoid hemorrhage. Neurocrit Care. 2014;20:84–90.
50. Vamvakas EC. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. Transfusion. 1995;35:760–8.
51. Nosotti M, Rebulla P, Riccardi D, et al. Correlation between perioperative blood transfusion and prognosis of patients subjected to surgery for stage I lung cancer. Chest. 2003;124:102–7.
52. Amato A, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. Cochrane Database Syst Rev 2006;CD005033.
53. Ng T, Ryder BA, Chern H, et al. Leukocyte-depleted blood transfusion is associated with decreased survival in resected early-stage lung cancer. J Thorac Cardiovasc Surg. 2012;143:815–9.
54. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA. 1998;279:217–21.
55. Leung JM, Weiskopf RB, Feiner J, et al. Electrocardiographic ST-segment changes during acute, severe isovolemic hemodilution in humans. Anesthesiology. 2000;93:1004–10.
56. Levy PS, Kim SJ, Eckel PK, et al. Limit to cardiac compensation during acute isovolemic hemodilution: influence of coronary stenosis. Am J Physiol. 1993;265:H340–9.
57. Ott DA, Cooley DA. Cardiovascular surgery in Jehovah's witnesses. Report of 542 operations without blood transfusion. JAMA. 1977;238:1256–8.
58. Slawson KB. Anaesthesia for the patient in renal failure. Br J Anaesth. 1972;44:277–82.
59. Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet. 1996;348:1055–60.
60. Spence RK, Carson JA, Poses R, et al. Elective surgery without transfusion: influence of preoperative hemoglobin level and blood loss on mortality. Am J Surg. 1990;159:320–4.
61. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340:409–17.
62. Lacroix J, Hebert PC, Hutchinson JS, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med. 2007;356:1609–19.
63. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11–21.

64. Carson J, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011;365:2453–62.

65. Walsh TS, Boyd JA, Watson D, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. Crit Care Med. 2013;41:2354–63.

66. Nikolsky E, Aymong ED, Halkin A, et al. Impact of anemia in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: analysis from the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial. J Am Coll Cardiol. 2004;44:547–53.

67. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). J Am Coll Cardiol. 2003;41:1933–9.

68. Kansagara D, Dyer E, Englander H, et al. Treatment of anemia in patients with heart disease. A systematic review. Ann Intern Med. 2013;159:746–57.

69. Chatterjee S, Wetterslev J, Sharma A, et al. Association of blood transfusion with increased mortality in myocardial infarction. A meta-analysis and diversity-adjusted study sequential analysis. JAMA Intern Med. 2013;173:132–9.

70. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA. 2004;292:1555–62.

71. Aronson D, Dann EJ, Bonstein L, et al. Impact of red blood cell transfusion on clinical outcomes in patients with acute myocardial infarction. Am J Cardiol. 2008;102:115–9.

72. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2012;157:49–58.

73. Qaseem A, Humphrey LL, Fitterman N, et al. Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2013;159:770–9.

74. Taylor Jr FB, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86:1327–30.

75. Gando S. Acute coagulopathy of trauma shock and coagulopathy of trauma: a rebuttal. You are now going down the wrong path. J Trauma. 2009;67:381–3.

76. Liumbruno G, Bennardello F, Lattanzio A, et al. Recommendations for the transfusion of plasma and platelets. Blood Transfus. 2009;7:132–50.

77. Khan H, Belsher J, Yilmaz M, et al. Fresh frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest. 2007;131:1308–14.

78. Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma. 2009;67:221–30.

79. Sarani B, Dunkman WJ, Dean L, et al. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med. 2008;36:1114–8.

80. Sorensen B, Fries D. Emerging treatment strategies for trauma-induced coagulopathy. Br J Surg. 2012;99 Suppl 1:40–50.

81. Davenport R, Curry N, Manson J, et al. Hemostatic effects of fresh frozen plasma may be maximal at red cell ratios of 1:2. J Trauma. 2011;70:90–5.

82. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. Anesth Analg. 2011;112:1289–95.

83. Torres LN, Sondeen JL, Ji L, et al. Evaluation of resuscitation fluids on endothelial glycocalyx, venular blood flow, and coagulation function after hemorrhagic shock in rats. J Trauma Acute Care Surg. 2013;75:759–66.

84. Dzik W, Rao A. Why do physicians request fresh frozen plasma? Transfusion. 2004;44:1393–4.

85. Dzik WH. The James Blundell Award Lecture 2006: transfusion and the treatment of haemorrhage: past, present and future. Transfus Med. 2007;17:367–74.

86. Segal JB, Dzik WH. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. Transfusion. 2005;45:1413–25.

87. Matevosyan K, Madden C, Barnett SL, et al. Coagulation factor levels in neurosurgical patients with mild prolongation of prothrombin time: effect on plasma transfusion therapy. J Neurosurg. 2011;114:3–7.

88. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: the effect of plasma transfusion on coagulation test results. Am J Clin Pathol. 2006;126:133–9.

89. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion. 2006;46:1279–85.

90. McCully SP, Fabricant LJ, Kunio NR, et al. The International Normalized Ratio overestimates coagulopathy in stable trauma and surgical patients. J Trauma Acute Care Surg. 2013;75:947–53.

91. Doerfler ME, Kaufman B, Goldenberg AS, et al. Central venous catheter placement in patients with disorders of hemostasis. Chest. 1996;110:185–8.

92. Mumtaz H, Williams V, Hauer-Jensen M, et al. Central venous catheter placement in patients with disorders of hemostasis. Am J Surg. 2000;180:503–5.

93. Fisher NC, Mutimer DJ. Central venous cannulation in patients with liver disease and coagulopathy—a prospective audit. Intensive Care Med. 1999;25:481–5.

94. Goldfarb G, Lebrec D. Percutaneous cannulation of the internal jugular vein in patients with coagulopathies: an experience based on 1,000 attempts. Anesthesiology. 1982;56:321–3.

95. Foster PF, Moore LR, Sankary HN, et al. Central venous catheterization in patients with coagulopathy. Arch Surg. 1992;127:273–5.

96. McVay PA, Toy PT. Lack of increased bleeding after paracentesis and thoracentesis in patients with mild coagulation abnormalities. Transfusion. 1991;31:164–71.

97. Hibbert RM, Atwell TD, Lekah A, et al. Safety of ultrasound-guided thoracentesis in patients with abnormal preprocedural coagulation parameters. Chest. 2013;144:456–63.

98. Runyon BA. Management of adult patients with ascites due to cirrhosis. Hepatology. 2004;39:841–56.

99. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133:160S–98S.

100. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy; antithrombotic therapy and prevention of thrombosis; 9th ed: American College of Chest Physicians Evidence-Based Clinical Practive Guidelines. Chest. 2012;141:e44s–88s.

101. Dezee KJ, Shimeall WT, Douglas KM, et al. Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. Arch Intern Med. 2006;166:391–7.

102. Hickey M, Gatien M, Taljaard M, et al. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. Circulation. 2013;128:360–4.

103. Pabinger I, Brenner B, Kalina U, et al. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. J Thromb Haemost. 2008;6:622–31.

104. Salman SS, Fernandez Perez ER, Stubbs JR, et al. The practice of platelet transfusion in the intensive care unit. J Intensive Care Med. 2007;22:105–10.

105. Levi M, Lowenberg EC. Thrpmbocytopenia in critically ill patients. Semin Thromb Hemost. 2008;34:417–24.

106. Moreau D, Timsit JF, Vesin A, et al. Platelet count decline: an early prognostic marker in critically ill patients with prolonged ICU stays. Chest. 2007;131:1735–41.

107. Akca S, Haji-Michael P, De MA, et al. Time course of platelet counts in critically ill patients. Crit Care Med. 2002;30:753–6.
108. Brogly N, Devos P, Boussekey N, et al. Impact of thrombocytopenia on outcome of patients admitted to ICU for severe community-acquired pneumonia. J Infect. 2007;55:136–40.
109. Priziola JL, Smythe MA, Dager WE. Drug-induced thrombocytopenia in critically ill patients. Crit Care Med. 2010;38:S145–54.
110. British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of platelet transfusions. Br J Haematol. 2003;122:10–23.
111. Slichter SJ. Platelet transfusion therapy. Hematol Oncol Clin North Am. 2007;21:697–729.
112. Martin M, Conlon LW. Does platelet transfusion improve outcomes in patients with spontaneous or traumatic intracerebral hemorrhage? Ann Emerg Med. 2013;61:58–61.
113. de Gans K, de Haan RJ, Majoie CB, et al. PATCH: platelet transfusion in cerebral haemorrhage: study protocol for a multicentre, randomised, controlled trial. BMC Neurol. 2010;10:19.
114. Warkentin TE, Greinacher A, Koster A, et al. Treatment and prevention of heparin-induced thrombocytopenia. American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest. 2008;133:340S–80S.
115. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med. 1996;101:502–7.
116. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e495S–530S.
117. Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost. 2006;4:759–65.
118. Tsai HM. Thrombotic thrombocytopenic purpura: a thrombotic disorder caused by ADAMTS13 deficiency. Hematol Oncol Clin North Am. 2007;21:609–32.
119. George JN. Thrombotic thrombocytopenic purpura. N Engl J Med. 2006;354:1927–35.
120. Kremer Hovinga JA, Meyer SC. Current management of thrombotic thrombocytopenic purpura. Curr Opin Hematol. 2008;15:445–50.
121. Pereira A, Mazzara R, Monteagudo J, et al. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome: a multivariate analysis of factors predicting the response to plasma exchange. Ann Hematol. 1995;70:319–23.
122. Cataland SR, Jin M, Lin S, et al. Cyclosporin and plasma exchange in thrombotic thrombocytopenic purpura: long-term follow-up with serial analysis of ADAMTS13 activity. Br J Haematol. 2007;139:486–93.
123. Callum JL, Karkouti K, Lin Y. Cryoprecipitate: the current state of knowledge. Transfus Med Rev. 2009;23:177–88.