

Esteban Gomez, Anurag K. Agrawal,
and Caroline A. Hastings

Contents

2.1	Introduction	27
2.2	Anemia	28
2.2.1	Red Blood Cell Transfusion Guidelines	28
2.2.2	Red Blood Cell Administration	29
2.3	Thrombocytopenia	30
2.3.1	Platelet Transfusion Guidelines	31
2.3.2	Platelet Administration	32
2.4	Granulocyte Transfusion	33
2.5	Risks of Blood Product Therapy and Their Management	33
2.5.1	Hemolytic Transfusion Reactions.....	34
2.5.2	Infection and Sepsis	34
2.5.3	Allergic Reactions/Anaphylaxis	36
2.5.4	Febrile Nonhemolytic Transfusion Reactions.....	36
2.5.5	Transfusion-Related Acute Lung Injury	36
2.5.6	Transfusion-Associated Circulatory Overload.....	37
2.5.7	Transfusion-Associated Graft- Versus-Host Disease.....	37
2.5.8	Iron Overload	37
2.6	Summary	38
	References	38

Abstract

The utilization of appropriate transfusion therapy is a vital aspect in the prevention of morbidity in pediatric oncology patients. Practitioners must be cognizant of the risks and benefits of transfusion as well as the appropriate transfusion practices in immunocompromised patients. Here we review the evidence regarding transfusion management practices in pediatric cancer patients with anemia, thrombocytopenia and neutropenia as well as practice in managing potential transfusion reactions. Where an evidence basis is lacking, we review consensus guidelines in both the pediatric and adult cohorts.

2.1 Introduction

The utilization of appropriate transfusion therapy is a vital aspect in the prevention of morbidity in pediatric oncology patients. Practitioners must be cognizant of the risks and benefits of transfusion as well as the appropriate transfusion practices in immunocompromised patients. Here we review the evidence regarding transfusion management practices in pediatric cancer patients with anemia, thrombocytopenia and neutropenia as well as practice in managing potential transfusion reactions. Where an evidence basis is lacking, we review consensus guidelines in both the pediatric and adult cohorts.

E. Gomez, MD • A.K. Agrawal, MD (✉)
C.A. Hastings, MD
Department of Hematology/Oncology,
Children's Hospital and Research Center Oakland,
747 52nd Street, Oakland, CA 94609, USA
e-mail: aagrawal@mail.cho.org

2.2 Anemia

Anemia is a deficiency of red blood cells (RBCs) and secondarily hemoglobin (hgb) concentration leading to a reduced oxygen-carrying capacity. Anemia is widely prevalent in pediatric oncology patients at presentation and during the course of their treatment. Studies document an overall incidence of anemia in >50 % of children with malignancy at diagnosis and during the course of treatment; as many as 97 % of those with pediatric leukemia have been reported to be affected (Green et al. 1998; Nachman et al. 1998; Hockenberry et al. 2002; Michon 2002). The specific hemoglobin concentration at which anemia becomes symptomatic is dependent on several variables including age, time over which anemia develops, and the clinical status of the patient and is usually unique to each individual patient. Understanding the etiology of anemia, its signs and symptoms and how it can be appropriately managed is essential to providing effective supportive care in the pediatric oncology patient.

Anemia develops due to suppressed erythropoiesis secondary to marrow infiltration with malignant cells, suppression related to chemotherapy, radiation therapy, or infection, impaired use of iron stores, and decreased endogenous erythropoietin (EPO) and blood loss secondary to hemorrhage, infection, repetitive blood sampling, and hemolysis (Groopman and Itri 1999; Cazzola 2000; Sobrero et al. 2001; Hockenberry et al. 2002; Stasi et al. 2003). Parvovirus B19, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) have specifically been reported to suppress erythropoiesis (Alpert and Fleisher 1984; Almeida-Porada and Ascensao 1996; El-Mahallawy et al. 2004; Eid et al. 2006). Recognition of the major contributors toward anemia can provide insight into the expected course and potential optimal interventions.

Clinical symptoms of anemia include fatigue, weakness, loss of appetite, headache, dizziness, irritability, fainting and poor concentration while signs of anemia include tachycardia, tachypnea, dyspnea, flow murmurs and, in severe cases, congestive heart failure (Cunningham 2003; Mock and Olsen 2003). The severity of signs and symptoms depends both on the degree of anemia and

the rapidity of decline. With a gradual onset, patient physiology has time to undergo compensatory changes that minimize symptoms. For example, the newly diagnosed leukemia patient often presents with severe anemia yet minimal symptoms. The gradual onset of anemia allows for physiologic compensation through plasma expansion and increased cardiac output allowing the patient to maintain near-normal activity despite profound decrement in hemoglobin concentration.

2.2.1 Red Blood Cell Transfusion Guidelines

The transfusion of packed red blood cells (PRBCs) is the primary treatment modality for anemia in pediatric oncology patients and provides rapid and relatively safe correction of anemia and its concurrent symptoms. Utilization of hematopoietic growth factors (i.e., recombinant erythropoietin, rhEPO) remains controversial and is discussed in Chap. 15; specific populations such as Jehovah's Witnesses, whose religious practice forbids the transfusion of blood products, may be able to avoid transfusion in certain cases with the utilization of rhEPO. The potential risk-benefit ratio of PRBC transfusion must be considered in each individual case and discussed with the patient and family; transfusion should therefore be avoided in the clinically stable child who is recovering from chemotherapy-induced aplasia. Evidence-based guidelines on appropriate thresholds for PRBC transfusion are lacking in the pediatric oncology literature since the decision to transfuse should be individualized (Buchanan 2005; Wong et al. 2005). Factors to consider include the effect of anemia on quality of life (i.e., fatigue, patient preference), cardiovascular stability, safety of procedures and sedation, the clinical condition of the patient, the presence or risk of bleeding, comorbidities such as infection and the anticipated length of suppressed erythropoiesis (Rossetto and McMahon 2000). Studies have demonstrated that adolescent and adult patients with higher hgb levels have improved quality of life measures (Hockenberry-Eaton and Hinds

Table 2.1 Red blood cell transfusion guidelines and level of evidence

Clinical status	Description	Hemoglobin level for transfusion (g/dL)	Level of evidence ^a
Stable	Asymptomatic, imminent marrow recovery	<7	1C
Vital sign changes	Tachycardia, tachypnea, hypotension	<8	1C
Thrombocytopenia	Recent or active hemorrhage	8–10	1C
Procedure	Potential blood loss	8–10	1C
	Anesthesia requirement	<7	1C
Oxygen requirement	Pulmonary or cardiac comorbidities	8–10	1C
Fatigue	Decreased quality of life, especially in adolescents	8–10	1B
Chronic anemia, infancy	Impact on growth or development	8–10	1C
Radiation therapy	Radiosensitizer	See text	2C

With permission from Agrawal et al. (2011)

^aPer Guyatt et al. (2006); see Preface

2000; Mock and Olsen 2003; Knight et al. 2004). Generally young children compensate for anemia better than adolescents and thus it is not uncommon for adolescents to have a higher hgb threshold at which they become symptomatic and at which transfusion should be considered (Davies and Kinsey 1994; Ruggiero and Riccardi 2002).

Generally, severe anemia (i.e., hgb <7 g/dL) is the threshold utilized for PRBC transfusion in pediatric oncology patients although may not be required for the well-compensated patient recovering from chemotherapy-induced aplasia (Table 2.1) (Ruggiero and Riccardi 2002; Marec-Berard et al. 2003). As expected, the need for PRBC transfusion is directly related to the intensity of therapy (Tas et al. 2002; Marec-Berard et al. 2003; Ruccione et al. 2012). Management of moderate anemia (i.e., hgb >7 g/dL) should be individualized based on physical findings, symptoms and patient preference; usually close monitoring is sufficient. Particular clinical situations may alter the threshold for PRBC transfusion: (1) the patient with planned surgery may require PRBC transfusion to minimize risks of induction anesthesia or blood loss; (2) the critically ill patient; (3) the patient with bleeding; (4) the patient with recent severe hemorrhage; and (5) the febrile patient with risk of sepsis and increased RBC and coagulation factor consumption (Table 2.1). Evidence is lacking to guide specific transfusion thresholds for each of these clinical situations and therefore provider and

institutional preference must be considered. Infants generally can be managed with the same hgb thresholds although underlying cardiopulmonary status, ability to feed, and effect on growth and development should be specifically considered (Roseff et al. 2002; Gibson et al. 2004). Utilization of PRBC transfusion for increased hgb thresholds in pediatric oncology patients with solid tumors receiving radiotherapy as a means to increase radiosensitivity remains controversial; see Chap. 13 for a summary of the evidence and recommendations which should occur in discussion with radiation oncology. Patients with leukemia and hyperleukocytosis (white blood cell [WBC] count >100 × 10⁹/L) are at risk for leukostasis secondary to the increase in the cytocrit. Often a compensatory decrease in the hgb (erythrocrit) is seen and may aid in the prevention of symptom development. Therefore, PRBC transfusion must be avoided in the asymptomatic patient with hyperleukocytosis; see Chap. 6 for a full discussion of PRBC transfusion with hyperleukocytosis.

2.2.2 Red Blood Cell Administration

Informed consent must be obtained prior to PRBC transfusion with a discussion of the risks, benefits and treatment alternatives to transfusion therapy. PRBCs are often stored in adsol (adenine saline, AS) secondary to a longer storage

life (42 days) with a resultant hematocrit of 55–60 % due to the addition of 100 mL of AS per unit blood. All pediatric oncology patients should receive leukoreduced, irradiated PRBCs. Leukocytes are implicated as contributory to the majority of transfusion reactions; leukoreduction has been shown to significantly reduce febrile nonhemolytic transfusion reactions (FNHTRs) as well as infection with viral, bacterial, and protozoal pathogens, and specifically CMV transmission (van Marwijk Kooy et al. 1991; Chu 1999; Vamvakas and Blajchman 2001; Dzik 2002; Heddle 2004; King et al. 2004; Paglino et al. 2004; Yazer et al. 2004; Blumberg et al. 2005). Although leukoreduction decreases CMV transmission, CMV-seronegative units are thought safer in at-risk populations; specifically for pediatric oncology, consensus guidelines recommend CMV-seronegative units in patients receiving hematopoietic stem cell transplantation (HSCT) although this recommendation is controversial (Hillyer et al. 1994; Blajchman et al. 2001; Nichols et al. 2003; Gibson et al. 2004; Ljungman 2004; Vamvakas 2005). Additional studies have shown no difference in CMV transmission rates in HSCT patients receiving leukoreduced versus CMV-seronegative PRBCs (Bowden et al. 1995; Thiele et al. 2011; Nash et al. 2012). PRBC irradiation is recommended in all immunocompromised patients to prevent transfusion-associated graft-versus-host disease (TA-GVHD) by inactivating donor T-cell replication and engraftment in the host (Anderson et al. 1991; Moroff and Luban 1992; Dwyre and Holland 2008; Rühl et al. 2009). Similar to HSCT-related GVHD, TA-GVHD can present with fever, anorexia, vomiting, diarrhea, skin rash, as well as pancytopenia and hepatic dysfunction. Directed donation of PRBCs from family members is generally not recommended due to the cost and time required in addition to not being shown more safe in the prevention of transfusion-associated infection (Strauss et al. 1990).

Determination of the goal hgb should direct the volume of PRBCs transfused and is dependent on the patient's clinical status, potential for ongoing blood loss and time to recovery from myelosuppressive chemotherapy. Generally 10–20 mL/kg of PRBCs are transfused, rounding

to the nearest unit to avoid blood product waste and historically given over 4 h although this practice is not well studied in hemodynamically stable children. In the patient without ongoing blood loss or alloimmunization, the expected rise in hgb is dependent on the hematocrit concentration of the PRBC product; for an AS preserved unit, the hgb is expected to increase by approximately 2 g/dL for each 10 mL/kg of PRBCs transfused (Davies et al. 2007). Anecdotal teaching that repeat hgb measurement must wait a certain period of time for reequilibration is poorly studied and likely unnecessary (Glatstein et al. 2005; Davies et al. 2007). Patients with severe chronic anemia (i.e., hgb <5 g/dL) are potentially at risk for transfusion-associated circulatory overload (TACO) due to the theoretical concern for cardiogenic pulmonary edema with transfusion in the patient with existing compensatory increase in plasma blood volume to near-normal levels. Variable practice exists, including slow transfusion of 5 mL/kg over 4 h, sometimes with the addition of a diuretic agent such as furosemide. Limited evidence suggests more liberal transfusion rates such as 2 mL/kg/h can be safely used in those patients without underlying evidence of hemodynamic instability or cardiopulmonary compromise (Jayabose et al. 1993; Agrawal et al. 2012).

2.3 Thrombocytopenia

Thrombocytopenia is a common side effect of intensive pediatric oncology therapy with potential risks for morbidity, dependent on the rate of platelet drop and seen more commonly when the platelet count is $<20 \times 10^9/L$ (Belt et al. 1978; Rintels et al. 1994). Petechiae, spontaneous hemorrhage and mucosal bleeding are common with platelet count $<20 \times 10^9/L$ while the risk for severe spontaneous or life-threatening hemorrhage is rare (Slichter and Harker 1978; Consensus Conference 1987; Gmür et al. 1991; Contreras 1998; Norfolk et al. 1998; Schiffer et al. 2001; Athale and Chan 2007). Thrombocytopenia occurs most commonly secondary to suppressed thrombopoiesis from chemotherapy,

Table 2.2 Platelet transfusion guidelines and level of evidence

Clinical scenario	Description	Platelet count for transfusion ($\times 10^9/L$)	Level of evidence ^a
Stable	Asymptomatic, imminent marrow recovery	<10	1B
Procedures	Diagnostic LP	50–100 (see text)	1B
	Subsequent LP	<20	1C
	Bone marrow aspiration	Not indicated	1C
	Minor surgery: central line placement, bronchoscopy with lavage, sinus aspiration, endoscopy with biopsy	<50	1C
	Major surgery: CNS or solid tumor resection or biopsy	<100	1C
Signs/symptoms or underlying diagnosis	Minor bleeding: epistaxis, mild mucosal bleeding	<20	1C
	Major bleeding: hemoptysis, hemorrhagic cystitis, GI, CNS, tumor necrosis	<100	1C
	Fever	<20	2C
	APL induction	<50	1C
	Newborns	<20–50	1C
	Radiation	<20–50	2C
	DIC	<50	1C
	Coagulopathy	<50	1C

LP lumbar puncture, CNS central nervous system, GI gastrointestinal, APL acute promyelocytic leukemia, DIC disseminated intravascular coagulation

With permission from Agrawal et al. (2011)

^aPer Guyatt et al. (2006); see Preface

radiation therapy or infection. Thrombocytopenia at diagnosis in leukemia patients can be secondary to marrow infiltration as well as splenic sequestration in those with splenomegaly. Increased platelet consumption can occur due to hemorrhage and sepsis with secondary disseminated intravascular coagulation (DIC). Frequent platelet transfusion increases the risk of developing platelet antibodies and subsequent refractoriness to further transfusion; therefore, as with PRBC transfusion, the risks and benefits of platelet transfusion must be considered in each individual case prior to the decision to transfuse.

2.3.1 Platelet Transfusion Guidelines

Platelet transfusion guidelines generally recommend prophylactic transfusion at threshold levels depending on the underlying risks of bleeding (Table 2.2). Although no specific pediatric oncology guidelines have been published, the American

Society of Clinical Oncology (ASCO) practice guidelines incorporate clinical trials in pediatric oncology (Schiffer et al. 2001). Factors that must be considered when deciding to transfuse platelets include: (1) cause of thrombocytopenia; (2) time to expected resolution; (3) rapidity of platelet count drop; (4) clinical condition of the patient including fever, infection, mucositis, coagulopathy or bleeding; (5) history of severe hemorrhage; (6) recent surgical procedure or planned surgery; and (7) concomitant medications such as amphotericin, enoxaparin and tyrosine kinase inhibitors.

Prospective, randomized trials in adolescents and adults with acute leukemia have reported that prophylactic transfusion can be safely given for a platelet threshold of $10 \times 10^9/L$ in clinically stable patients (Gmür et al. 1991; Heckman et al. 1997; Rebulla et al. 1997; Wandt et al. 1998).

What platelet threshold is appropriate for patients undergoing procedures, for those with a history of hemorrhage and in those with potential concurrent bleeding risk factors such as fever,

infection, and coagulopathy has not been well studied. Similarly, social factors such as distance to clinic and ease of accessing care must also be considered when determining the need for platelet transfusion (Benjamin and Anderson 2002). Although definitive evidence is lacking, consensus panels have concluded that platelets $>50 \times 10^9/L$ and $>20 \times 10^9/L$ are sufficient for major and minor surgical procedures, respectively (Norfolk et al. 1998; Rebulla 2001; Schiffer et al. 2001; BCSH 2003). Risk of bleeding has been found to correlate most with a history of severe hemorrhage rather than platelet count (Friedmann et al. 2002).

What platelet threshold should be utilized for lumbar puncture in pediatric oncology patients is poorly studied. One large retrospective study concluded that a platelet threshold of $>10 \times 10^9/L$ was sufficient for lumbar puncture (LP) although only 3.8 % of patients had platelet count $<20 \times 10^9/L$ at the time of LP (Howard et al. 2000). A follow-up study analyzing risk factors for traumatic LP concluded that African American race, age <1 year, prior traumatic tap within 2 weeks, prior LP with platelets $<50 \times 10^9/L$, lack of general anesthesia, platelet count $<100 \times 10^9/L$, interval of <15 days between LPs and a less experienced practitioner were all significant (Howard et al. 2002). What effect this analysis has on practice is unclear. The study was also confounded by a high rate of traumatic (29.3 %; ≥ 10 RBC/ μL) and bloody (10.4 %; ≥ 500 RBC/ μL) LPs (Howard et al. 2002). Based on this analysis the authors conclude that a platelet count $>100 \times 10^9/L$ should be the threshold for diagnostic LP and the procedure be performed by the most experienced practitioner (Howard et al. 2002). Data on the prognostic significance of traumatic LP and theoretical potential of introduction of leukemic blasts into the cerebrospinal fluid are controversial although multiple studies have shown it to be a risk factor for poor outcome (Gajjar et al. 2000; Bürger et al. 2003; te Loo et al. 2006). Whether a lower platelet count in the hands of an experienced practitioner remains a risk factor for traumatic LP is unknown.

Unlike LP procedures, bone marrow aspiration and biopsy can be performed without regard

to platelet count as long as pressure is applied to the area after the procedure (BCSH 2003). For patients undergoing central line placement, adult studies have shown that platelet counts >30 – $50 \times 10^9/L$ are safe (Stellato et al. 1985; Coit and Turnbull 1988; Lowell and Bothe 1991; Barrera et al. 1996; Doerfler et al. 1996; Ray and Shenoy 1997; Loh and Chui 2007). No similar studies have been reported in pediatric patients. Additionally, the need for a particular platelet count for some post-procedure time period to prevent development of bleeding has not been reported.

2.3.2 Platelet Administration

Platelets for transfusion come as either pooled platelet concentrates (PPCs) or as an apheresis unit. PPCs are aggregated from red blood cell donations and contain $\geq 5.5 \times 10^{10}$ platelets. Four to six platelet units are combined to make a PPC. On the other hand, an apheresis platelet unit is obtained from a single donor and is the equivalent of 6–10 PC units (i.e., $\geq 3 \times 10^{11}$ platelets). Transfusion with apheresis platelets minimizes exposure to multiple blood donors although whether this decreases the risk of alloimmunization and therefore is of benefit in patient populations requiring frequent transfusion such as pediatric oncology is controversial (NEJM 1997). Apheresis platelet units undergo leukodepletion during the collection procedure, whereas PPCs must be subsequently filtered. Leukodepletion has been shown to decrease the risk of alloimmunization in both PPCs and apheresis units (NEJM 1997). Risk of bacterial contamination is low with both PPCs and apheresis units and has not been found to be significantly different (Schrezenmeier et al. 2007). Storage of platelet units at 20–24 °C with gentle horizontal agitation has been found safe up to 5 days after collection; longer storage times increase the risk for bacterial proliferation and cytokine-mediated reactions (Schiffer et al. 1986; Klein et al. 1997).

As with PRBCs, platelets should be dosed by weight with 10 mL/kg of either PPCs or an apheresis product resulting in an increase of

50–100 × 10⁹/L (Roseff et al. 2002; Fasano and Luban 2008). Determination of response as well as clinical status of the patient can guide future transfusions; generally patients are not given more than one apheresis unit although those with a poor response to transfusion or active bleeding may require higher doses. Platelets are transfused over 30–60 min although more rapid infusion rates have been found safe and effective (Norville et al. 1997). Although considered a risk factor, a direct relationship between number of transfused platelet units and incidence of platelet refractoriness has not been consistently shown in the literature (Howard and Perkins 1978; Dutcher et al. 1981; Schiffer et al. 2001). Platelet refractoriness is defined as an insufficient platelet increment after transfusion on at least two occasions and is the most significant long-term complication of platelet transfusion (Schiffer 1991). ABO incompatibility has been shown to be a risk factor in development of platelet refractoriness (Carr et al. 1990). HLA-matched platelets and crossmatching have been shown effective in improving platelet increment in patients found refractory (Duquesnoy et al. 1977; Heal et al. 1987; Kickler et al. 1988; Welch et al. 1989; O'Connell et al. 1992; Friedberg et al. 1993, 1994; Gelb and Leavitt 1997). As with PRBCs, platelets should be irradiated to prevent TA-GVHD in immunocompromised patients, while CMV seronegativity may be unnecessary in the apheresis product for the CMV-seronegative patient (Luban et al. 2000; Nichols et al. 2003; Dwyre and Holland 2008).

2.4 Granulocyte Transfusion

Patients with prolonged neutropenia are at increasing risk of infection and secondarily lack neutrophils to eradicate infection. Therefore it has been theorized that frequent granulocyte transfusion may be an effective method to fight serious infection in the severely neutropenic patient without imminent count recovery. Although theoretically promising and potentially shown beneficial in small observational studies, consistent data are lacking and some meta-analyses have failed to show a significant benefit

(Vamvakas and Pineda 1997; Bishton and Chopra 2004; Robinson and Marks 2004; Grigull et al. 2006; Sachs et al. 2006; van de Wetering et al. 2007; Seidel et al. 2008; Massey et al. 2009; Peters 2009).

In the patient with severe, refractory or progressive bacterial or fungal infection and severe neutropenia likely to continue >1 week, granulocyte transfusion can be considered (Bishton and Chopra 2004). Donors should be mobilized with G-CSF and dexamethasone with a goal transfusion dose of >1.0 × 10⁹ cells/kg in the pediatric patient transfused daily for a minimum of 4–7 days (Chanock and Gorlin 1996; Klein et al. 1996; Massey et al. 2009). Granulocyte transfusion should be ABO compatible and crossmatched as well as irradiated to prevent TA-GVHD (Bishton and Chopra 2004). CMV-seronegative products should be used in CMV-seronegative patients to prevent CMV transmission (Bishton and Chopra 2004).

2.5 Risks of Blood Product Therapy and Their Management

In the past, clerical error leading to ABO-incompatible blood transfusion and secondary acute hemolysis, as well as infectious complications, were the most common transfusion reactions (Williamson et al. 1999; Linden et al. 2000; Myhre and McRuer 2000; Stainsby et al. 2006). Now, due to improved blood safety, transfusion-related acute lung injury (TRALI) has become most common in the adult literature due to increased recognition, and generally noninfectious causes are much more common (Bolton-Maggs and Murphy 2004; Stainsby et al. 2006). Reactions to transfusion may range from mild to life-threatening and the clinician must be able to promptly recognize the potential severe reaction in the face of common transfusion-related symptoms such as fever. Acute reactions are defined as occurring within 24 h while delayed reactions occur beyond the acute period. Potential reactions include acute and delayed hemolysis, FNHTR, allergic reactions, TRALI, TACO, TA-GVHD

and infectious complications. In the chronically transfused, alloimmunization to PRBC transfusion must be considered in addition to iron overload. Management of transfusion reactions is generally based on best practice and consensus guidelines rather than an evidence basis (Table 2.3).

2.5.1 Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions (AHTRs) present with fever, chills, nausea and vomiting as well as anxiety and discomfort. Additional signs and symptoms include dyspnea, hypotension or shock, oliguria, hemoglobinuria, hemoglobinemias and disseminated intravascular coagulation (DIC). AHTRs generally occur secondary to IgM antibodies to anti-A and anti-B isohemagglutinins but may additionally develop due to other IgM and IgG antibodies. Bystander hemolysis can secondarily lyse recipient red blood cells. AHTR is generally due to ABO incompatibility but may also occur with other immune and nonimmune causes including RBCs damaged by blood warmers, incorrectly prepared frozen PRBCs, bacterial contamination, as well as autoimmune and drug-induced causes of hemolysis. Delayed hemolytic transfusion reactions (DHTRs) present with milder symptoms including low-grade fever, jaundice, and a lower than expected posttransfusion hgb increment and are due to previously sensitized patients without detectable antibody at the time of crossmatch. DHTR occurs with IgG antibody-mediated complement fixation, manifesting as extravascular hemolysis.

Evaluation of a potential AHTR should include each blood unit transfused. Laboratory evaluation involves repeat crossmatch, performance of a direct antibody test (DAT; direct Coombs), as well as measurement of hgb, urinalysis, and plasma-free hgb or haptoglobin. With a more insidious DHTR leading to extravascular hemolysis, laboratory assessment should include hgb, reticulocyte count, DAT, indirect bilirubin and lactate dehydrogenase. Management of an AHTR is based on best practice and includes

immediately stopping the transfusion, providing fluid support, and monitoring perfusion and urine output. Vasopressor support may be required as well as management of DIC with platelets and fresh frozen plasma (FFP). Transfusion of additional PRBCs should be avoided due to the potential for continued bystander hemolysis but can be given in the symptomatic patient or if with continued active bleeding.

2.5.2 Infection and Sepsis

Transfusion-transmitted viral infections have markedly decreased with improved donor screening and viral testing measures; current estimated rates of transmission include approximately <1 in 1.5 million for HIV, 1 in 300,000 for hepatitis B virus, and <1 in 2 million for hepatitis C virus (Busch et al. 2005; Dodd 2007; Dwyre et al. 2011). Advanced serologic screening measures have decreased the window period in which viral transmission has recently transpired but without positive testing measures, although, false-negative tests can still occur (Dwyre et al. 2011). Posttransfusion hepatitis is generally caused by viruses including hepatitis A, B, C and E in addition to CMV and EBV. CMV transmission can lead to primary infection in the previously CMV-seronegative recipient or reactivation in the previously infected recipient. CMV can lead to a mononucleosis-type syndrome and immunocompromised patients are at risk for more severe manifestations including nephritis, retinitis, interstitial pneumonitis, colitis and cytopenias (Rubin et al. 1985). Additional rare transmission of human T-lymphotropic retrovirus, human herpesvirus-8 and variant Creutzfeldt-Jakob disease has been noted (Dodd 2007). Parvovirus B19 is not routinely screened and can cause a prolonged reticulocytopenia and anemia in patients with underlying hematologic malignancies (Kaur and Basu 2005).

Bacterial infection must be considered in the patient with a new fever or fever increase ≥ 1 °C from the previous 24 h during transfusion. Blood contamination can occur at the time of collection or during processing and has decreased

Table 2.3 Management guidelines for transfusion reactions and level of evidence

Type	Clinical features	Lab/imaging findings	Management	Level of evidence ^a
Acute hemolytic transfusion reaction (AHTR)	Immediate onset; fever, anxiety, hypotension, DIC, renal failure	↑Indirect bilirubin Hematuria ↑LDH/AST ↓Haptoglobin ↑Plasma-free hgb +DAT	Stop transfusion	1C
			ICU support	
			Fluid resuscitation	
			Vasopressor support	
			FFP, platelets for DIC	
			Avoid PRBC transfusion	
			Diuretics to maintain urine output once BP stabilized	
Febrile nonhemolytic transfusion reaction (FNHTR)	During or within 4 h of transfusion; fever, chills, rigors, nausea/vomiting, headache	None	Stop transfusion	1C
			Rule out AHTR and bacterial contamination/sepsis	
			Antipyretics	
			Restart transfusion if serious adverse reactions ruled out	
Allergic transfusion reaction	Immediate for severe reaction with anaphylaxis (i.e., bronchospasm, hypotension); during or following transfusion for mild reaction (i.e., urticaria, pruritus)	None	Stop transfusion	1C
			Severe reaction: epinephrine, diphenhydramine, H ₂ blocker, consider steroid	
			Mild reaction: diphenhydramine	
Delayed hemolytic transfusion reaction (DHTR)	>24 h from transfusion and within 2 weeks; fever, chills, jaundice, malaise; can be asymptomatic	↓Hgb vs expected posttfn increment ↑Bilirubin ↑LDH +DAT +Red cell alloantibodies	Usually no treatment required	1C
			Potential repeat tfn	
			Screen for new red cell antibodies	
Transfusion-related acute lung injury (TRALI)	Within 6 h of transfusion; dyspnea, hypoxemia, fever, hypotension, noncardiogenic pulmonary edema	+CXR with diffuse infiltrates	Oxygen	1C
			Vasopressor support	
			Mechanical ventilation	
			Unclear benefit for corticosteroids	
Bacterial sepsis	Usually of immediate onset if severe GNR; fever, chills, rigors, hypotension, DIC, oliguria, shock	+Bcx from patient and/or transfusion bag	Stop transfusion	1C
			Fluid resuscitation	
			ICU support	
			Vasopressors	
			Empiric antibiotics with ceftaz/tobra	

DIC disseminated intravascular coagulation, *bili* bilirubin, *LDH* lactate dehydrogenase, *AST* aspartate aminotransferase, *DAT* direct antiglobin test [Coombs], *ICU* intensive care unit, *FFP* fresh frozen plasma, *PRBC* packed red blood cell, *BP* blood pressure, *hgb* hemoglobin, *CXR* chest radiograph, *GNR* Gram-negative rods, *Bcx* blood culture
Adapted from Agrawal et al. (2011)

^aPer Guyatt et al. (2006); see Preface

significantly with improved blood collection and screening procedures (Wagner 1997; Kuehnert et al. 2001; Stainsby et al. 2006; Dodd 2007). Bacterial infection is much more common with

platelets compared to PRBCs since they are stored at room temperature and risk of contamination has been directly correlated to storage time (Morrow et al. 1991). Fatal infection is more

likely due to Gram-negative endotoxin production as compared to the more commonly seen Gram-positive organisms (Arduino et al. 1989). Transfusion should be stopped in the event of fever or signs or symptoms of sepsis. The patient should be treated immediately with volume resuscitation, broad spectrum antibiotics and a transfusion workup commenced including blood cultures of the transfusion bag.

2.5.3 Allergic Reactions/ Anaphylaxis

Allergic reactions are common, complicating 1–5 % of transfusions and more likely with platelet or plasma transfusion (Couban et al. 2002). Reactions are type I hypersensitivity mediated and usually mild with cutaneous manifestations although systemic symptoms related to anaphylaxis are possible and usually occur within minutes of transfusion commencement. Transfusion should be held once allergic symptoms manifest; diphenhydramine is usually sufficient to manage cutaneous symptoms. In the case of systemic symptoms consistent with anaphylaxis, the transfusion should not be restarted and the patient may require additional medications including epinephrine, steroids and fluid expansion. Any patient with a systemic reaction should be evaluated for IgA deficiency. Prophylaxis with diphenhydramine in the patient with a previous reaction has not been shown beneficial although it is often utilized (Wang et al. 2002; Sanders et al. 2005; Geiger and Howard 2007; Kennedy et al. 2008). It is reasonable to consider prophylactic corticosteroids prior to transfusion in the patient with multiple reactions; if symptoms continue, or if the patient is IgA deficient, washed blood products should be utilized.

2.5.4 Febrile Nonhemolytic Transfusion Reactions

FNHTR is defined as a temperature increase of $\geq 1^\circ\text{C}$ associated with transfusion and not attrib-

utable to any other cause. FNHTR was common prior to the advent of leukoreduction due to pyrogenic cytokines released from leukocytes during storage (Heddle et al. 1993; King et al. 2004; Paglino et al. 2004; Yazer et al. 2004). A recent study of transfusions in a pediatric intensive care unit reported a 0.9 % rate of FNHTRs (Gauvin et al. 2006). FNHTR is a diagnosis of exclusion and therefore transfusion should be halted until an AHTR has been ruled out. Additional diagnostic considerations should include bacterial contamination and TRALI. Fever related to FNHTR can occur during or up to 4 h after the completion of transfusion and is self-limited. Antipyretics can be provided for comfort and the transfusion restarted once the patient has defervesced and more serious causes have been ruled out. The utilization of antipyretics to prevent the development of FNHTR has shown little benefit, even in the patient with a history of FNHTRs (Wang et al. 2002; Sanders et al. 2005; Geiger and Howard 2007; Kennedy et al. 2008). Notwithstanding, prophylactic antipyretics can be considered in the patient with multiple FNHTRs although may not be effectual; washed blood products can be considered with continued FNHTR.

2.5.5 Transfusion-Related Acute Lung Injury

TRALI is an increasingly recognized life-threatening complication which occurs after transfusion of plasma-containing blood products (Popovsky 2000; Bolton-Maggs and Murphy 2004; Stainsby et al. 2006). In a 2004 consensus conference, TRALI was defined as acute lung injury occurring within 6 h of transfusion without any other potential causes (Kleinman et al. 2004; Andreu 2009). Symptoms of TRALI include dyspnea, tachypnea and fever; signs include hypotension, hypoxemia and bilateral infiltrates on chest radiograph without fluid overload (Kleinman et al. 2004). A paucity of data exist in pediatric patients although it appears that the pathogenesis and course are similar to adult

patients, with the majority recovering in 48–96 h after the precipitating event (Sanchez and Toy 2005; Church et al. 2006). Although the pathophysiology of TRALI is yet to be clearly delineated, passive transfer of antibody leading to neutrophil activation in the lung is thought the most likely mechanism, exacerbated in those with existing lung injury and therefore less likely in pediatric patients (Popovsky 2000; Goldman et al. 2005). Fresh frozen plasma is the most likely contributing blood product, especially when the donor is an antibody-positive multiparous female (Eder et al. 2007). Increasing platelet age at time of transfusion has also been noted as a risk factor (Silliman et al. 2003).

TRALI is a diagnosis of exclusion and patients with mild symptoms may improve without TRALI being recognized. Patients will require oxygen support and some will need mechanical ventilation and vasopressor support. Corticosteroids may be of benefit as with other causes of acute lung injury but are unproven in TRALI (Barrett and Kam 2006). Recognition of TRALI is vital in order to provide the appropriate medical management and also to potentially screen for neutrophil-specific antibodies.

2.5.6 Transfusion-Associated Circulatory Overload

TACO is also becoming increasingly recognized although is a rare phenomenon in pediatric patients with normal underlying cardiorespiratory function. TACO is defined as cardiogenic pulmonary edema and is due to too large a transfusion volume or too rapid a transfusion rate (Eder et al. 2007). Clinical signs and symptoms of TACO include dyspnea, tachypnea, hypoxemia and hypertension as compared to the hypotension seen in TRALI. Hypertension is due to a positive fluid balance with pulmonary and systemic overcirculation and therefore unlike TRALI, the patient with TACO should be managed with aggressive diuresis. In the patient not responding to diuresis, other potential diagnoses should be entertained.

2.5.7 Transfusion-Associated Graft-Versus-Host Disease

In the immunocompromised patient, nonirradiated blood and platelet products can lead to TA-GVHD, especially in the setting of histocompatible donor T cells. Manifestations of TA-GVHD are similar to GVHD seen secondary to allogeneic HSCT and include fever, anorexia, vomiting and diarrhea, and skin rash of variable presentation and severity. Pancytopenia and hepatic dysfunction may be present. The patient should be diagnosed by skin biopsy, liver biopsy or bone marrow aspirate and may require life-saving HSCT.

2.5.8 Iron Overload

Total body iron is closely regulated in order to maintain a steady state load of 35–45 mg/kg (Shander et al. 2009). Iron absorption from food intake is extremely limited (i.e., 1 mg/day) as are mechanisms of iron excretion; therefore, when patients receive frequent PRBC transfusion with the receipt of approximately 1 mg of iron per 1 mL of transfused blood, iron overload can occur, resulting in non-transferrin-bound iron (i.e., free iron) and subsequent free iron deposition in tissues, specifically parenchymal cells of the liver, heart, pancreas and endocrine tissues (Shander et al. 2009; de Ville de Goyet et al. 2013). Free iron may also be associated with oxidative damage due to generation of free oxygen radicals, likely accentuated in the setting of concomitant chemotherapy delivery (Shander et al. 2009).

Iron overload leads to a higher incidence of organ failure and mortality in populations that are chronically transfused and has also been noted as a risk factor for mortality in oncology patients with myelodysplastic syndrome (MDS) and in those receiving HSCT (Ballas 2001; Cazzola and Malcovati 2005; Darbari et al. 2006; Malcovati et al. 2006; Armand et al. 2007; Garcia-Manero et al. 2008; Fenaux and Rose 2009; Shander et al. 2009; Alessandrino et al. 2010). In pediatric

oncology, studies have shown that transfusion burden increases with increased therapy intensity in both hematologic malignancies and solid tumor patients leading to iron overload in more than half of patients although the effect of this iron overload on subsequent toxicities is poorly quantified (Emy et al. 1997; Eng and Fish 2011; Ruccione et al. 2012; de Ville de Goyet et al. 2013). Quantification of total body iron can be assessed by liver biopsy, measurement with a superconducting quantum interference device (SQUID) or more recently through proton magnetic resonance imaging (Fischer et al. 1999; Angelucci et al. 2000; Brittenham et al. 2001; St Pierre et al. 2005; Wood et al. 2005).

Iron overload may be a factor in late effects in long-term survivors of pediatric cancers and therefore all patients should be screened at the end of therapy for potential iron overload. Patients who have received >1 g of transfused iron (>4 units PRBCs) should be screened with a serum ferritin level and transferrin saturation (Halonen et al. 2003). For patients with serum ferritin levels persistently >1,000 ng/mL, measurement of total body iron stores by proton MRI should be considered. In such cases chelation therapy or serial phlebotomy should also be a consideration, especially in the adolescent male.

2.6 Summary

Blood product transfusion is a common practice in patients undergoing myelosuppressive therapy. That being said, an evidence basis for PRBC and platelet thresholds for transfusion are generally lacking and therefore consensus guidelines, assessment of each individual patient and the underlying clinical situation, as well as patient preference must all be routine considerations in the decision to transfuse. Prior to transfusion, the patient, family and practitioner must all be aware of the potential short- and long-term risks of transfusion. The practitioner should be able to determine the appropriate volume and preparative steps required for transfusion and the likely increment in hgb or platelet count after transfusion. Any potential concerning reaction during a

transfusion should be appropriately managed and assessed per standard guidelines, as described.

References

- Agrawal AK, Hastings CH, Feusner J (2011) Hematologic supportive care in children with cancer. In: Pizzo PA, Poplack DG (eds) Principles and practice of pediatric oncology, 6th edn. Lippincott Williams and Wilkins, Philadelphia
- Agrawal AK, Hsu E, Quirolo K et al (2012) Red blood cell transfusion in pediatric patients with severe chronic anemia: how slow is necessary. *Pediatr Blood Cancer* 58:466–468
- Alessandrino EP, Della Porta MG, Bacigalupo A et al (2010) Prognostic impact of pre-transplantation transfusion history and secondary iron overload in patients with myelodysplastic syndrome undergoing allogeneic stem cell transplantation: a GITMO study. *Haematologica* 95:476–484
- Almeida-Porada GD, Ascensao JL (1996) Cytomegalovirus as a cause of pancytopenia. *Leuk Lymphoma* 21:217–223
- Alpert G, Fleisher GR (1984) Complications of infection with Epstein-Barr virus during childhood: a study of children admitted to the hospital. *Pediatr Infect Dis* 3:304–307
- Anderson KC, Goodnough LT, Sayers M et al (1991) Variation in blood component irradiation practice: implications for prevention of transfusion-associated graft-versus-host disease. *Blood* 77:2096–2102
- Andreu G (2009) Transfusion-associated circulatory overload and transfusion-related acute lung injury: diagnosis, pathophysiology, management and prevention. *ISBT Sci Ser* 4:63–71
- Angelucci E, Brittenham GM, McLaren CE et al (2000) Hepatic iron concentration and total body iron stores in thalassemia major. *N Engl J Med* 343:327–331
- Arduino MJ, Bland LA, Tipple MA et al (1989) Growth and endotoxin production of *Yersinia enterocolitica* and *Enterobacter agglomerans* in packed erythrocytes. *J Clin Microbiol* 27:1483–1485
- Armand P, Kim HT, Cutler CS et al (2007) Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. *Blood* 109:4586–4588
- Athale UH, Chan AK (2007) Hemorrhagic complications in pediatric hematologic malignancies. *Semin Thromb Hemost* 33:408–415
- Ballas SK (2001) Iron overload is a determinant of morbidity and mortality in adult patients with sickle cell disease. *Semin Hematol* 38:30–36
- Barrera R, Mina B, Huang Y et al (1996) Acute complications of central line placement in profoundly thrombocytopenic cancer patients. *Cancer* 78:2025–2030

- Barrett NA, Kam PC (2006) Transfusion-related acute lung injury: a literature review. *Anesthesia* 61:777–785
- Belt RJ, Leite C, Haas CD, Stephens RL (1978) Incidence of hemorrhagic complications in patients with cancer. *JAMA* 239:2571–2574
- Benjamin RJ, Anderson KS (2002) What is the proper threshold for platelet transfusion in patients with chemotherapy-induced thrombocytopenia? *Crit Rev Oncol Hematol* 42:163–171
- Bishton M, Chopra R (2004) The role of granulocyte transfusions in neutropenic patients. *Br J Haematol* 127:501–508
- Blajchman MA, Goldman M, Freedman JJ, Sher GD (2001) Proceedings of a consensus conference: prevention of post-transfusion CMV in the era of universal leukoreduction. *Transfus Med Rev* 15:1–20
- Blumberg N, Fine L, Gettings KF, Heal JM (2005) Decreased sepsis related to indwelling venous access devices coincident with implementation of universal leukoreduction of blood transfusions. *Transfusion* 45:1632–1639
- Bolton-Maggs PH, Murphy MF (2004) Blood transfusion. *Arch Dis Child* 89:4–7
- Bowden RA, Slichter SJ, Sayers M et al (1995) A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. *Blood* 86:3598–3603
- British Committee for Standards in Hematology (BCSH) (2003) Guidelines on the use of platelet transfusions. *Br J Haematol* 122:10–23
- Brittenham GM, Sheth S, Allen CJ et al (2001) Noninvasive methods for quantitative assessment of transfusional iron overload in sickle cell disease. *Semin Hematol* 38:37–56
- Buchanan GR (2005) Blood transfusions in children with cancer and hematologic disorders: why, when, and how? *Pediatr Blood Cancer* 44:114–116
- Bürger B, Zimmermann M, Mann G et al (2003) Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or traumatic lumbar puncture. *J Clin Oncol* 21:184–188
- Busch MP, Glynn SA, Stramer SL (2005) A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. *Transfusion* 45:254–264
- Carr R, Hutton JL, Jenkins JA et al (1990) Transfusion of ABO-mismatched platelets leads to early platelet refractoriness. *Br J Haematol* 75:408–413
- Cazzola M (2000) Mechanisms of anaemia in patients with malignancy: implications for the clinical use of recombinant human erythropoietin. *Med Oncol* 17:S11–S16
- Cazzola M, Malcovati L (2005) Myelodysplastic syndromes—coping with ineffective hematopoiesis. *N Engl J Med* 352:536–538
- Chanock SJ, Gorlin JB (1996) Granulocyte transfusions. Time for a second look. *Infect Dis Clin North Am* 10:327–343
- Chu RW (1999) Leukocytes in blood transfusion: adverse effects and their prevention. *Hong Kong Med J* 5:280–284
- Church GD, Price C, Sanchez R (2006) Transfusion-related acute lung injury in the paediatric patient: two case reports and a review of the literature. *Transfus Med* 16:343–348
- Coit DB, Turnbull AD (1988) A safe technique for the placement of implantable vascular access devices in patients with thrombocytopenia. *Surg Gynecol Obstet* 167:429–431
- Consensus Conference (1987) Platelet transfusion therapy. *JAMA* 257:1777–1780
- Contreras M (1998) The appropriate use of platelets: an update from the Edinburgh Consensus Conference. *Br J Haematol* 101:10–12
- Couban S, Carruthers J, Andreou P et al (2002) Platelet transfusion in children: results of a randomized, prospective, crossover trial of plasma removal and a prospective audit of WBC reduction. *Transfusion* 42:753–758
- Cunningham RS (2003) Anemia in the oncology patient: cognitive function and cancer. *Cancer Nurs* 26:38S–42S
- Darbari DS, Kple-Faget P, Kwagyan J et al (2006) Circumstances of death in adult sickle cell disease patients. *Am J Hematol* 81:858–863
- Davies SC, Kinsey SE (1994) Clinical aspects of paediatric blood transfusion: cellular components. *Vox Sang* 67:50–53
- Davies P, Robertson S, Hedge S et al (2007) Calculating the required transfusion volume in children. *Transfusion* 47:212–216
- De Ville de Goyet M, Moniotte S, Robert A et al (2013) Iron overload in children undergoing cancer treatments. *Pediatr Blood Cancer* 60:1982–1987
- Dodd RY (2007) Current risk for transfusion transmitted infections. *Curr Opin Hematol* 14:671–676
- Doerfler ME, Kaufman B, Goldenberg AS (1996) Central venous catheter placement in patients with disorders of hemostasis. *Chest* 110:185–188
- Duquesnoy RJ, Filip DJ, Rodey GE et al (1977) Successful transfusion of platelets “mis-matched” for HLA antigens to alloimmunized thrombocytopenic patients. *Am J Hematol* 2:219–226
- Dutcher JP, Schiffer CA, Aisner J et al (1981) Alloimmunization following platelet transfusion: the absence of a dose–response relationship. *Blood* 57:395–398
- Dwyre DM, Holland PV (2008) Transfusion-associated graft-versus-host disease. *Vox Sang* 95:85–93
- Dwyre DM, Fernando LP, Holland PV (2011) Hepatitis B, hepatitis C and HIV transfusion-transmitted infections in the 21st century. *Vox Sang* 100:92–98
- Dzik WH (2002) Leukoreduction of blood components. *Curr Opin Hematol* 9:521–526
- Eder AF, Herron R, Strupp A et al (2007) Transfusion-related acute lung injury surveillance (2003–2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. *Transfusion* 47:599–607

- Eid AJ, Brown RA, Patel R, Razonable RR (2006) Parvovirus B19 infection after transplantation: a review of 98 cases. *Clin Infect Dis* 43:40–48
- El-Mahallawy HA, Mansour T, El-Din SE et al (2004) Parvovirus B19 infection as a cause of anemia in pediatric acute lymphoblastic leukemia patients during maintenance chemotherapy. *J Pediatr Hematol Oncol* 26:403–406
- Emy PY, Levin TL, Sheth SS et al (1997) Iron overload in reticuloendothelial systems of pediatric oncology patients who have undergone transfusions: MR observations. *Am J Radiol* 168:1011–1015
- Eng J, Fish JD (2011) Insidious iron burden in pediatric patients with acute lymphoblastic leukemia. *Pediatr Blood Cancer* 56:368–371
- Fasano R, Luban NL (2008) Blood component therapy. *Pediatr Clin North Am* 55:421–455
- Fenaux P, Rose C (2009) Impact of iron overload in myelodysplastic syndromes. *Blood Rev* 23:S15–S19
- Fischer R, Tiemann ED, Engelhardt R et al (1999) Assessment of iron stores in children with transfusion siderosis by biomagnetic liver susceptometry. *Am J Hematol* 60:289–299
- Friedberg RC, Donnelly SF, Boyd JC et al (1993) Clinical and blood bank factors in the management of platelet refractoriness and alloimmunization. *Blood* 81:3428–3434
- Friedberg RC, Donnelly SF, Mintz PD (1994) Independent roles for platelet crossmatching and HLA in the selection of platelets for alloimmunized patients. *Transfusion* 34:215–220
- Friedmann AM, Sengul H, Lehmann H et al (2002) Do basic laboratory tests or clinical observations predict bleeding in thrombocytopenic oncology patients? A reevaluation of prophylactic platelet transfusions. *Transfus Med Rev* 16:34–45
- Gajjar A, Harrison PL, Sandlund JT et al (2000) Traumatic lumbar puncture at diagnosis adversely affects outcome in childhood acute lymphoblastic leukemia. *Blood* 96:3381–3384
- Garcia-Manero G, Shan J, Faderl S et al (2008) A prognostic score for patients with low risk myelodysplastic syndrome. *Leukemia* 22:538–543
- Gauvin F, Lacroix J, Robillard P et al (2006) Acute transfusion reactions in the pediatric intensive care unit. *Transfusion* 46:1899–1908
- Geiger TL, Howard SC (2007) Acetaminophen and diphenhydramine premedication for allergic and febrile nonhemolytic transfusion reactions: good prophylaxis or bad practice? *Transfus Med Rev* 21:1–12
- Gelb AB, Leavitt AD (1997) Crossmatch-compatible platelets improve corrected count increments in patients who are refractory to randomly selected platelets. *Transfusion* 37:624–630
- Gibson BE, Todd A, Roberts I et al (2004) Transfusion guidelines for neonates and older children. *Br J Haematol* 124:433–453
- Glatstein M, Oron T, Barak M et al (2005) Posttransfusion equilibration of hematocrit in hemodynamically stable neonates. *Pediatr Crit Care Med* 6:707–708
- Gmür J, Burger J, Schanz U et al (1991) Safety of stringent prophylactic platelet transfusion policy for patients with acute leukaemia. *Lancet* 338:1223–1226
- Goldman M, Webert KE, Arnold DM et al (2005) Proceedings of a consensus conference: towards an understanding of TRALI. *Transfus Med Rev* 19:2–31
- Green DM, Breslow NE, Beckwith JB et al (1998) Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the National Wilms' Tumor Study Group. *J Clin Oncol* 16:237–245
- Grigull L, Pulver N, Goudeva L et al (2006) G-CSF mobilised granulocyte transfusions in 32 paediatric patients with neutropenic sepsis. *Support Care Cancer* 14:910–916
- Groopman JE, Itri LM (1999) Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst* 91:1616–1634
- Guyatt G, Gutterman D, Baumann MH et al (2006) Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 129:174–181
- Halonen P, Mattila J, Suominen P et al (2003) Iron overload in children who are treated for acute lymphoblastic leukemia estimated by liver siderosis and serum iron parameters. *Pediatrics* 111:91–96
- Heal JM, Blumberg N, Masel D (1987) An evaluation of crossmatching, HLA, and ABO matching for platelet transfusions to refractory patients. *Blood* 70:23–30
- Heckman KD, Weiner GJ, Davis CS et al (1997) Randomized study of prophylactic platelet transfusion threshold during induction therapy for adult acute leukemia: 10,000/microL versus 20,000/microL. *J Clin Oncol* 15:1143–1149
- Heddle NM (2004) Universal leukoreduction and acute transfusion reactions: putting the puzzle together. *Transfusion* 44:1–4
- Heddle NM, Klama LN, Griffith L et al (1993) A prospective study to identify the risk factors associated with acute reactions to platelet and red cell transfusion. *Transfusion* 33:794–797
- Hillyer CD, Emmens RK, Zago-Novaretti M, Berkman EM (1994) Methods for the reduction of transfusion-transmitted cytomegalovirus infection: filtration versus the use of seronegative donor units. *Transfusion* 34:929–934
- Hockenberry MJ, Hinds PS, Barrera P et al (2002) Incidence of anemia in children with solid tumors or Hodgkin disease. *J Pediatr Hematol Oncol* 24:35–37
- Hockenberry-Eaton M, Hinds PS (2000) Fatigue in children and adolescents with cancer: evolution of a program of study. *Semin Oncol Nurs* 16:261–272
- Howard JE, Perkins HA (1978) The natural history of alloimmunization to platelets. *Transfusion* 18:496–503
- Howard SC, Gajjar AC, Ribeiro RC et al (2000) Safety of lumbar puncture for children with acute

- lymphoblastic leukemia and thrombocytopenia. *JAMA* 284:2222–2224
- Howard SC, Gajjar AC, Cheng C et al (2002) Risk factors for traumatic and bloody lumbar puncture in children with acute lymphoblastic leukemia. *JAMA* 288:2001–2007
- Jayabose S, Tugal O, Ruddy R et al (1993) Transfusion therapy for severe anemia. *Am J Pediatr Hematol Oncol* 15:324–327
- Kaur P, Basu S (2005) Transfusion-transmitted infections: existing and emerging pathogens. *J Postgrad Med* 51:146–151
- Kennedy LD, Case LD, Hurd DD et al (2008) A prospective, randomized, double-blind controlled trial of acetaminophen and diphenhydramine pretransfusion medication versus placebo for the prevention of transfusion reactions. *Transfusion* 48:2285–2291
- Kickler TS, Ness PM, Baine HG (1988) Platelet cross-matching. A direct approach to the selection of platelet transfusions for the alloimmunized thrombocytopenic patient. *Am J Clin Pathol* 90:69–72
- King KE, Shirey RS, Thoman SK et al (2004) Universal leukoreduction decreases the incidence of febrile non-hemolytic transfusion reactions to RBCs. *Transfusion* 44:25–29
- Klein HG, Strauss RG, Schiffer CA (1996) Granulocyte transfusion therapy. *Semin Hematol* 33:359–368
- Klein HG, Dodd RY, Ness PM et al (1997) Current status of microbial contamination of blood components: summary of a conference. *Transfusion* 37:95–101
- Kleinman S, Caulfield T, Chan P et al (2004) Towards an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* 44:1774–1789
- Knight K, Wade S, Balducci L (2004) Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *Am J Med* 116:11S–26S
- Kuehnert MJ, Roth VR, Haley NR et al (2001) Transfusion-transmitted bacterial infection in the United States, 1998 through 2000. *Transfusion* 41:1493–1499
- Linden JV, Wagner K, Voytovich AE et al (2000) Transfusion errors in New York state: an analysis of 10 years' experience. *Transfusion* 40:1207–1213
- Ljungman P (2004) Risk of cytomegalovirus transmission by blood products to immunocompromised patients and means for reduction. *Br J Haematol* 125:107–116
- Loh AH, Chui CH (2007) Port-A-Cath insertions in acute leukemia: dose thrombocytopenia affect morbidity? *J Pediatr Surg* 42:1180–1184
- Lowell JA, Bothe A Jr (1991) Venous access. Preoperative, operative, and postoperative dilemmas. *Surg Clin North Am* 71:1231–1246
- Luban NL, Drothler D, Moroff G et al (2000) Irradiation of platelet components: inhibition of lymphocyte proliferation assessed by limiting-dilution analysis. *Transfusion* 40:348–352
- Malcovati L, Della Porta MG, Cazzola M (2006) Predicting survival and leukemic evolution in patients with myelodysplastic syndrome. *Haematologica* 91:1588–1590
- Marec-Berard P, Blay JY, Schell M et al (2003) Risk model predictive of severe anemia requiring RBC transfusion after chemotherapy in pediatric solid tumor patients. *J Clin Oncol* 21:4235–4238
- Massey E, Paulus U, Doree C et al (2009) Granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction. *Cochrane Database Syst Rev* (1):CD005341
- Michon J (2002) Incidence of anemia in pediatric cancer patients in Europe: results of a large, international survey. *Med Pediatr Oncol* 39:448–450
- Mock V, Olsen M (2003) Current management of fatigue and anemia in patients with cancer. *Semin Oncol Nurs* 19:36–41
- Moroff G, Luban NL (1992) Prevention of transfusion-associated graft-versus-host disease. *Transfusion* 32:102–103
- Morrow JF, Braine HG, Kickler TS et al (1991) Septic reactions to platelet transfusions. A persistent problem. *JAMA* 266:555–558
- Myhre BA, McRuer D (2000) Human error—a significant cause of transfusion mortality. *Transfusion* 40:879–885
- Nachman J, Sather HN, Cherlow JM et al (1998) Response of children with high-risk acute lymphoblastic leukemia treated with and without cranial irradiation: a report from the Children's Cancer Group. *J Clin Oncol* 16:920–930
- Nash T, Hoffmann S, Butch S et al (2012) Safety of leukoreduced, cytomegalovirus (CMV)-untested components in CMV-negative allogeneic human progenitor cell transplant recipients. *Transfusion* 52:2270–2272
- Nichols WG, Price TH, Gooley T et al (2003) Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. *Blood* 101:4195–4200
- Norfolk DR, Ancliffe PJ, Contreras M et al (1998) Consensus Conference on Platelet Transfusion, Royal College of Physicians of Edinburgh, 27–28 November 1997. Synopsis of background papers. *Br J Haematol* 101:609–617
- Norville R, Hinds P, Wilimas J et al (1997) The effects of infusion rate on platelet outcomes and patient responses in children with cancer: an in vitro and in vivo study. *Oncol Nurs Forum* 24:1789–1793
- O'Connell BA, Lee EJ, Rothko K et al (1992) Selection of histocompatible apheresis platelet donors by cross-matching random donor platelet concentrates. *Blood* 79:527–531
- Paglini JC, Pomper GJ, Fisch GS et al (2004) Reduction of febrile but not allergic reactions to RBCs and platelets after conversion to universal prestorage leukoreduction. *Transfusion* 44:16–24
- Peters C (2009) Granulocyte transfusions in neutropenic patients: beneficial effects proven? *Vox Sang* 96:275–283
- Popovsky MA (2000) Transfusion-related acute lung injury. *Curr Opin Hematol* 7:402–407

- Ray CE Jr, Shenoy SS (1997) Patients with thrombocytopenia: outcome of radiologic placement of central venous access devices. *Radiology* 204:97–99
- Rebulla P (2001) Platelet transfusion trigger in difficult patients. *Transfus Clin Biol* 8:249–254
- Rebulla P, Finazzi G, Marangoni F et al (1997) The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia. Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto. *N Engl J Med* 337:1870–1875
- Rintels PB, Kenney RM, Crowley JP (1994) Therapeutic support of the patient with thrombocytopenia. *Hematol Oncol Clin North Am* 8:1131–1157
- Robinson SP, Marks DI (2004) Granulocyte transfusion in the G-CSF era. Where do we stand? *Bone Marrow Transplant* 34:839–846
- Roseff SD, Luban NL, Manno CS (2002) Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion* 42:1398–1413
- Rossetto CL, McMahon JE (2000) Current and future trends in transfusion therapy. *J Pediatr Oncol Nurs* 17:160–170
- Rubin RH, Tolkoff-Rubin NE, Oliver D et al (1985) Multicenter seroepidemiologic study of the impact of cytomegalovirus infection on renal transplantation. *Transplantation* 40:243–249
- Ruccione KS, Midambi K, Sposto R et al (2012) Association of projected transfusional iron burden with treatment intensity in childhood cancer survivors. *Pediatr Blood Cancer* 59:697–702
- Ruggiero A, Riccardi R (2002) Interventions for anemia in pediatric cancer patients. *Med Pediatr Oncol* 39:451–454
- Rühl H, Bein G, Sachs UJ (2009) Transfusion-associated graft-versus-host disease. *Transfus Med Rev* 23: 62–71
- Sachs UJ, Reiter A, Walter T et al (2006) Safety and efficacy of therapeutic early onset granulocyte transfusions in pediatric patients with neutropenia and severe infections. *Transfusion* 46:1909–1914
- Sanchez R, Toy P (2005) Transfusion related acute lung injury: a pediatric perspective. *Pediatr Blood Cancer* 45:248–255
- Sanders RP, Maddirala SD, Geiger TL et al (2005) Premedication with acetaminophen or diphenhydramine for transfusion with leucoreduced blood products in children. *Br J Haematol* 130:781–787
- Schiffer CA (1991) Prevention of alloimmunization against platelets. *Blood* 77:1–4
- Schiffer CA, Lee EJ, Ness PM et al (1986) Clinical evaluation of platelet concentrates stored for one to five days. *Blood* 67:1591–1594
- Schiffer CA, Anderson KC, Bennett CL et al (2001) Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 19:1519–1538
- Schrezenmeier H, Walther-Wenke G, Müller TH et al (2007) Bacterial contamination of platelet concentrates: results of a prospective multicenter study comparing pooled whole blood-derived platelets and apheresis platelets. *Transfusion* 47:644–652
- Seidel MG, Peters C, Wacker A et al (2008) Randomized phase III study of granulocyte transfusions in neutropenic patients. *Bone Marrow Transplant* 42: 679–684
- Shander A, Cappellini MD, Goodnough LT (2009) Iron overload and toxicity: the hidden risk of multiple blood transfusions. *Vox Sang* 97:185–197
- Silliman CC, Boshkov LK, Mehdizadehkashi Z et al (2003) Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood* 101:454–462
- Slichter SJ, Harker LA (1978) Thrombocytopenia: mechanisms and management of defects in platelet production. *Clin Haematol* 7:523–539
- Sobrero A, Puglisi F, Guglielmi A et al (2001) Fatigue: a main component of anemia symptomatology. *Semin Oncol* 28:15–18
- St Pierre TG, Clark PR, Chau-anusorn W et al (2005) Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood* 105:855–861
- Stainsby D, Jones H, Asher D et al (2006) Serious hazards of transfusion: a decade of hemovigilance in the UK. *Transfus Med Rev* 20:273–282
- Stasi R, Abriani L, Beccaglia P et al (2003) Cancer-related fatigue: evolving concepts in evaluation and treatment. *Cancer* 98:1786–1801
- Stellato TA, Gauderer MW, Lazarus HM et al (1985) Percutaneous silastic catheter insertion in patients with thrombocytopenia. *Cancer* 56:2691–2693
- Strauss RG, Barnes A Jr, Blanchette VS et al (1990) Directed and limited-exposure blood donations for infants and children. *Transfusion* 30:68–72
- Tas F, Eralp Y, Basaran M et al (2002) Anemia in oncology practice: relation to diseases and their therapies. *Am J Clin Oncol* 25:371–379
- te Loo DM, Kamps WA, van der Does-van den Berg A et al (2006) Prognostic significance of blasts in the cerebrospinal fluid without pleiocytosis or a traumatic lumbar puncture in children with acute lymphoblastic leukemia: experience of the Dutch Childhood Oncology Group. *J Clin Oncol* 24:2332–2336
- The Trial to Reduce Alloimmunization to Platelets Study Group (1997) Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *N Engl J Med* 337:1861–1869
- Thiele T, Krüger W, Zimmermann K et al (2011) Transmission of cytomegalovirus (CMV) infection by leukoreduced blood products not tested for CMV antibodies: a single-center prospective study in high-risk patients undergoing allogeneic hematopoietic stem cell transplantation (CME). *Transfusion* 51: 2620–2626
- Vamvakas EC (2005) Is white blood cell reduction equivalent to antibody screening in preventing transmission of cytomegalovirus by transfusion? A review of

- the literature and meta-analysis. *Transfus Med Rev* 19:181–199
- Vamvakas EC, Blajchman MA (2001) Universal WBC reduction: the case for and against. *Transfusion* 41:691–712
- Vamvakas ED, Pineda AA (1997) Determinants of the efficacy of prophylactic granulocyte transfusions: a meta-analysis. *J Clin Apher* 12:74–81
- van de Wetering MD, Weggelaar N, Offinga M et al (2007) Granulocyte transfusions in neutropaenic children: a systematic review of the literature. *Eur J Cancer* 43:2082–2092
- van Marwijk Kooy M, van Prooijen HC, Moes M et al (1991) Use of leukocyte-depleted platelet concentrates for the prevention of refractoriness and primary HLA alloimmunization: a prospective, randomized trial. *Blood* 77:201–205
- Wagner S (1997) Transfusion-related bacterial sepsis. *Curr Opin Hematol* 4:464–469
- Wandt H, Frank M, Ehninger G et al (1998) Safety and cost effectiveness of a $10^3 \times 10(9)/L$ trigger for prophylactic platelet transfusions compared with the traditional $20^3 \times 10(9)/L$ trigger: a prospective comparative trial in 105 patients with acute myeloid leukemia. *Blood* 91:3601–3606
- Wang SE, Lara PN, Lee-Ow A et al (2002) Acetaminophen and diphenhydramine as premedication for platelet transfusions: a prospective randomized double-blind placebo-controlled trial. *Am J Hematol* 70:191–194
- Welch HG, Larson EB, Slichter SJ (1989) Providing platelets for refractory patients. Prudent strategies. *Transfusion* 29:193–195
- Williamson LM, Lowe S, Love EM et al (1999) Serious hazards of transfusion (SHOT) initiative: analysis of the first two annual reports. *BMJ* 319:16–19
- Wong EC, Perez-Albuerne E, Moscow JA, Luban NL (2005) Transfusion management strategies: a survey of practicing pediatric hematology/oncology specialists. *Pediatr Blood Cancer* 44:119–127
- Wood JC, Enriquez C, Ghugre N et al (2005) MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. *Blood* 106:1460–1465
- Yazer MH, Podlosky L, Clarke G, Nahirniak SM (2004) The effect of prestorage WBC reduction on the rates of febrile nonhemolytic transfusion reactions to platelet concentrates and RBC. *Transfusion* 44:10–15

Supportive Care in Pediatric Oncology

A Practical Evidence-Based Approach

Feusner, J.; Hastings, C.A.; Agrawal, A.K. (Eds.)

2015, X, 304 p. 18 illus., 9 illus. in color., Hardcover

ISBN: 978-3-662-44316-3