Review article

Intraoperative pediatric blood transfusion therapy: a review of common issues. Part II: transfusion therapy, special considerations, and reduction of allogenic blood transfusions

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Introduction

Part two of this paper reviews transfusion therapy with a focus upon massive blood transfusion, new strategies for the treatment of massive transfusion therapy, specific situations where transfusion may be anticipated in pediatric patients, and a brief overview for strategies to reduce allogenic blood transfusions.

III: Transfusion therapy

A. Massive blood transfusion and coagulopathy

Massive blood transfusion is defined as the loss of one or more circulating blood volumes. It is, therefore, important to calculate the patient’s estimated blood volume (EBV) and to relate this to the volume of blood products and other fluids administered (Table 1). In addition the anesthesiologist should estimate how much blood will be allowed to be lost before the initiation of packed RBC transfusion. The patient’s EBV is generally related in part to the patient’s age as well as body habitus. Younger patients have a higher fraction of their weight as blood while more obese patients have a lower fraction. Once the patient’s circulating blood volume has been estimated then a further simple calculation allows estimation of the maximal allowable blood loss (MABL). A simple mathematical calculation is:

\[
MABL = \frac{(\text{starting hematocrit} - \text{target hematocrit})}{\text{starting hematocrit}} \times \text{EBV}
\]

For example, if the child weighs 25 kg there will be a circulating blood volume of 70 ml x 25 kg = \(\sim1750\) ml. If that child also has a starting hematocrit of 36% and the target hematocrit is 21% then the following calculation applies:

\[
MABL = \frac{(36 - 21)}{36} \times 1750 = \sim 730\text{ml}
\]

This shed blood can be replaced with a balanced salt solution such as lactated Ringer’s solution in a volume of 3 : 1, i.e. \(\sim2200\) ml or with 5% albumen 1 : 1 or hetastarch 1 : 1, i.e. 730 ml. Once the estimated blood loss reaches this target value then RBC cell transfusion should be initiated. Obviously preterm and term infants, children with cyanotic congenital heart disease, large ventilation/perfusion mismatch, high metabolic demand, and children with respiratory failure, may benefit from having the hematocrit

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maintained at a higher target value. Conversely, children in countries with poor blood product screening may benefit from avoiding transfusion until a much lower target hematocrit, e.g. ~5 g·dl⁻¹.

Since the hematocrit in packed RBCs is approximately 70%, each 100 ml of packed RBCs transfused will provide 70 ml of RBCs. In the example given above, if the blood loss exceeded the MABL by 150 ml and assuming that the target hematocrit was 30%, then replacement would be made according to the following formula:

(i) volume of blood to replace (150 ml) × desired hematocrit (30%) = 45 ml of 100% RBCs;
(ii) the approximate hematocrit in packed RBCs is 70%;
(iii) therefore, 45 ml ÷ 0.70 = approximately 65 ml of packed RBCs;
(iv) 65 ml of packed RBCs (~hematocrit 70%) is equivalent to 150 ml of (whole) blood with a hematocrit of 30%.

This can usually be simplified by transfusing approximately 0.5 ml packed RBCs for each millilitre of blood loss beyond the MABL; this will result in a slightly higher hematocrit than the target 30% but since all of these calculations are estimates the end result is usually close to the desired value.

The coagulopathy of massive blood transfusion is caused by both a reduction in platelets (dilutional thrombocytopenia) and a reduction in clotting factors. In general, a good rule of thumb is that a patient will lose approximately 40% of the starting platelet count with the first blood volume lost, another 20% of the starting platelet count with the second blood volume lost, and approximately 10% of the starting platelet count with the third blood volume lost (Figure 1) (1). Thus at three blood volumes lost with no platelet replacement, the platelet count would be expected to be reduced by approximately 70% from baseline values (1). This emphasizes why it is so vital to have a baseline platelet count when massive blood loss is anticipated since patients who begin with a low platelet count are at risk for pathological bleeding even after only one blood volume loss whereas those who start with an abnormally high platelet count may not require transfusion despite blood loss equivalent to four or five circulating blood volumes (1).

The coagulopathy secondary to dilution of clotting factors depends upon the type and volume of transfused blood product. Whole blood contains all clotting factors including fibrinogen at normal values except for the labile factors (FV and FVIII); even these factors are present in 20–50% of their normal values. Therefore with transfusion of whole blood, despite reduced amounts of the labile clotting factors (FV and FVIII), pathological coagulation generally does not occur until three or more blood volumes have been lost (2–4). However, such large quantities of whole blood are rarely used with modern blood banking, instead the blood loss is replaced with albumen, starch, crystalloid, and packed RBCs. With this type of replacement multiple clotting factor deficiencies will appear much earlier since approximately 80% of the coagulation factors have been separated into the plasma fraction. In this situation, clotting factor deficiency should be anticipated once blood loss exceeds one blood volume (Table 2).

The evaluation of coagulopathy depends in part on the availability of specific laboratory tests that can be rapidly returned to the anesthesiologist so as to allow the intraoperative evaluation of specific abnormalities of coagulation. The simplest approach, when

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Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Estimated blood volume (ml·kg⁻¹)</th>
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</thead>
<tbody>
<tr>
<td>Premature infant</td>
<td>90–100</td>
</tr>
<tr>
<td>Term infant – 3 months</td>
<td>80–90</td>
</tr>
<tr>
<td>Children older than 3 months</td>
<td>70</td>
</tr>
<tr>
<td>Very obese children</td>
<td>65</td>
</tr>
</tbody>
</table>

Figure 1

Serial changes in platelet counts as a percent of baseline (mean ± SD) in 26 children who lost one to three blood volumes during surgery and did not receive exogenous platelets. Patients whose platelet counts were ≥50 × 10⁹ l⁻¹ did not exhibit clinically important bleeding [modified from (1)].
laboratory tests are slow to return or unavailable, is simply drawing a sample of blood into a blood tube without anticoagulant and observing the rapidity of clot formation and the presence or absence of clot lysis. A clot should form in 4–8 min and there should be no clot lysis if all coagulation parameters are within normal limits and there is no coagulopathy. A platelet count will provide a reference number to indicate the need to increase platelets via transfusion therapy. Generally, in a normal patient a platelet count >50,000 mm$^3$ does not require treatment unless further blood loss is expected. Obviously cardiac bypass is a different situation where platelets become dysfunctional due to the trauma of the bypass machine. A prothrombin time (PT) will provide global information regarding the so-called extrinsic clotting system (factors VII, X, V, prothrombin and fibrinogen); an acceptable value would be an INR of <1.5 (less than 1.5 times normal). An activated partial thromboplastin time (PTT) provides global information regarding the so-called intrinsic clotting system (factors XII, XI, IX, VIII, X, V, prothrombin and fibrinogen); a value <50 s (less than 1.5 times normal) does not generally require treatment. The presence of a significant increase in fibrin split products combined with a low fibrinogen value generally indicates disseminated intravascular coagulopathy. In this situation, cryoprecipitate or fresh frozen plasma may provide the needed increase in factors. More sophisticated tests such as the platelet function analyzer (PFA) will provide a measure of platelet function that is more reliable than bleeding times in children. Thromboelastography (TEG) will provide information regarding the rapidity of clot formation and clot lysis as well as a rapid means for determining the effectiveness of each intervention. Neither PFA nor TEG have been found to have a positive predictive value for perioperative bleeding in most settings. Management of specific coagulation abnormalities such as hemophilia and von Willebrand disease are beyond the scope of this review but new approaches to coagulation are presented below.

Table 3 presents our indications for monitoring based upon the anticipated blood loss. Recent advances in transfusion therapy such as the development of recombinant clotting factor replacement therapy may dramatically alter our current approach to patients undergoing massive blood transfusions resulting in either dilutional thrombocytopenia or multiple clotting factor deficiencies. Such therapy will allow specific clotting factor replacement and reduce exposure to homologous blood products and the potential for disease transmission or transfusion reactions.

### B. Recombinant factor VIIa

A novel but at present enormously expensive approach to treat bleeding is the use of recombinant factor VIIa (rFVIIa) (NovoSeven®, Novo Nordisk Pharmaceutical Inc., Princeton, NJ, USA). This product was developed for the management of bleeding complications in hemophilia patients who also have alloantibodies against factors VIII and IX (5–8). However, it is likely that further research will find many additional indications for patients with coagulopathy from a variety of causes (Figure 2) (9). The current model of the coagulation cascade is based upon the observation that formation of a tissue factor-factor VIIa complex (TF-FVIIa) is the major initiating event of in vivo hemostasis (Figure 3). This paradigm differs from the traditional coagulation cascade involving separate intrinsic and extrinsic pathways and helps to explain the importance of the presence of adequate amounts of critical factors (i.e. VII, X, V, VIII and XI) while deficiencies of others (i.e. XII) do not result in clinical bleeding. Tissue factor is normally located deep within vessel walls and is not usually exposed to the general circulation until an injury occurs. Injury to tissue results in release of TF from the endothelium. Tissue factor then forms a complex with activated factor VII (VII → VIIa). Factor VIIa in turn activates factor X (X → Xa) and prothrombin, which promotes the production of thrombin and the formation of fibrin clots at the site of injury (10). It appears that rFVIIa...
also activates factors IX and X on the surface of activated platelets (IX → IXa & X → Xa), leading to the generation of additional amounts of thrombin (11–17). Activated platelets serve as a surface site for activation of factors VIII (VIII → VIIIa), and XIa, as well as further interaction with activated factors X and V (V → Va) to create thrombin. Effective hemostasis requires full thrombin generation in the presence of activated platelets. Thus rFVIIa administration promotes hemostasis at several locations within the coagulation cascade and may be useful in normal patients as well as patients with thrombocytopenia (18–20).

The pharmacokinetics of rFVIIa have been most extensively studied in patients with hemophilia. It is important to note that the half-life of rFVIIa is shorter (1.3 vs. 2.7 h) and the clearance faster (67 vs. 37 ml·kg⁻¹·h⁻¹) in pediatric patients compared with adults (21). There may also be differences in patients who have ongoing blood loss compared with hemophilia patients (21). Studies of small numbers of cirrhotic patients and those undergoing liver transplant have revealed altered pharmacokinetics as well (21). Initial dosing regimens for hemophiliacs undergoing surgery include an intravenous dose of 90–120 μg·kg⁻¹ of rFVIIa (22). Studies completed in trauma and surgical patients have used somewhat higher dosing (up to 200 μg·kg⁻¹) (23). Follow-up dosing intervals of 2–4 h because of the relatively short circulating half

Table 3
Estimated predicted blood loss and recommended monitoring and equipment

<table>
<thead>
<tr>
<th>Predicted blood loss</th>
<th>Recommended monitors/equipment</th>
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<tbody>
<tr>
<td>&lt;0.5 blood volumes</td>
<td>Routine monitoring</td>
</tr>
<tr>
<td>0.5–1.0 blood volumes</td>
<td>Routine monitoring + urine catheter</td>
</tr>
<tr>
<td>1.0 blood volumes or greater</td>
<td>Routine monitoring + urine catheter + CVP + arterial line</td>
</tr>
<tr>
<td>1.0 blood volumes or greater with potential for rapid blood loss</td>
<td>Routine monitoring + urine catheter + CVP + arterial line + large bore IV + rapid infusion device</td>
</tr>
<tr>
<td>Severe head injury</td>
<td>Routine monitoring + urine catheter + CVP + arterial line + large bore IV + rapid infusion device</td>
</tr>
<tr>
<td>Major trauma with unknown severity</td>
<td>Routine monitoring + urine catheter</td>
</tr>
</tbody>
</table>


Figure 2
Proposed likely indications for the use of recombinant factor VIIa (NovoSeven®). Note that this agent is not yet approved for use in children except for the treatment of hemophilia von Willebrand disease with high titer inhibitors or for congenital factor VII deficiency. However many clinical trials in adults and anecdotal reports in children suggest potential use for a wide variety of conditions resulting in pathological bleeding. See text for details. Modified from (9).
life of NovoSeven, adds considerably to the expense of using this agent.

Satisfactory hemostasis with rFVIIa administration has been achieved in critically ill massively transfused trauma victims, patients undergoing cardiopulmonary bypass, those sustaining liver injury or undergoing liver transplantation, as well as uncontrolled gastrointestinal or intraabdominal hemorrhage (16, 24–32). Neurosurgical patients with coagulopathy have also received benefit from rFVIIa administration in order to correct coagulopathy prior to surgical intervention to evacuate intracranial bleeding (33).

The use of rFVIIa has been shown in adults to decrease prothrombin time and increase hemostasis at the site of injury (34–36). The sensitivity of plasma assays such as the prothrombin time (PT) to even the smallest quantities of activated factor VII do not correlate with clinical outcomes and thus makes these tests unsuitable for monitoring responses to rFVIIa therapy (37). A more promising strategy has been the use of TEG. These whole blood assays measure several aspects of effective hemostasis, including the rate of thrombin generation, as well as fibrin clot strength, elasticity and degradation in the presence of activated platelets (38–40). This approach has been far more reliable in measuring responses to rFVIIa in hemophilia patients with high-titer factor VIII inhibitors, in normal subjects, and has also been used for monitoring anticoagulation therapy.

The administration of rFVIIa provides the advantage of hemostasis at the site of injury, without systemic activation of the coagulation cascade (11–16, 41). Although rFVIIa has proven useful in multiple situations, at the time of this writing, it is not United States Food and Drug Administration (FDA) approved for use in trauma or surgical procedures. The initial intention and only FDA approved use is for patients with hemophilia or von Willebrand disease who have developed inhibitor antibodies or patients with congenital factor VII deficiency. There are limited pediatric data at this point but anecdotal cases suggest some promise for treating a variety of conditions with pathological bleeding (27, 33, 42–51). Because rFVIIa uses recombinant technology, no material of human origin or blood product is used in its production (17).
therefore, may aid in the control of surgical bleeding
in Jehovah’s Witness patients and help to avoid
transfusion. It also is less immunogenic and eliminates
the risk of viral or bacterial contamination that
can occur with blood product transfusion. It would
appear that this new weapon for treating coagulopa-
ythy will be available to anesthesiologists in the near
future. It is also likely that the cost of such treatment
will be quite enormous thus mandating very clear
indications. Potential concerns regarding the recom-
binant products are allergic reactions, inhibitor
formation, and thromboses (6).

C. Platelet infusions

In general, most pediatric patients will have platelet
counts within the normal range at the time surgery is
needed, however, those with chronic inflammatory
diseases and patients with functional or surgical
asplenia may have high platelet counts. Patients
with infections, on myelosuppressive chemotherapy,
or those with ongoing coagulopathies will be at
risk for thrombocytopenia. For patients who are
otherwise normal, a platelet count greater than
50 000 mm\(^{-3}\) is required in order to maintain hemo-
stasis (1). Patients who are chronically thrombo-
cytopenic will often not manifest bleeding
tendencies even when the platelet count is in the
10 000–20 000 mm\(^{-3}\) range. Immune or nonimmu-
nological-based peripheral platelet destruction may
shorten the survival of transfused platelets. None-
theless, perioperative platelet transfusions may be
appropriate if significant bleeding is anticipated. In
these patients a preoperative transfusion plan
should be developed in consultation with the child’s
oncologist/hematologist.

IV: Specific circumstances

A. Trauma

Trauma related injuries are the leading cause of
death in pediatric patients. Exsanguination, either at
the site of the accident, or in the hospital, accounts
for 39% of all traumatic deaths (52). The major
source of morbidity and mortality in pediatric
trauma victims is oxygen deprivation to vital organs.
Because both anemia and hypovolemia decrease
oxygen delivery, appropriate transfusion and
volume resuscitation are critical. Although rapid
infusion of fluids to a trauma patient who is
hemorrhagic and hypotensive may seem obvious,
the end points for fluid administration to hemody-
namically stable victims of blunt trauma and severe
head injury are vague and not well established. The
overtransfusion of such patients may result in
cerebral edema, pulmonary edema, or coagulopathy.

The evaluation and treatment of the pediatric
trauma patient differs from that of the adult primar-
ily because of differences in physiology. The evalua-
tion of the volume status of the pediatric trauma
patient may be difficult since children are able to
maintain a normal blood pressure in a supine
condition with a loss of up to 20% of their blood
volume. In pediatric trauma victims, postural hypo-
tension and a narrow pulse pressure may be more
sensitive signs of hypovolemia than tachycardia or
systolic hypotension. Invasive monitors can be
extremely helpful in this population, and should
never be omitted secondary to patient size. The
insertion of an arterial line greatly facilitates beat to
beat blood pressure monitoring while a central
venous line provides valuable information regarding
cardiac filling pressures particularly when the blood
loss is such that it cannot be quantitated, e.g. internal
bleeding, neurosurgical trauma. Our experience has
been that a 2–3 mmHg reduction in the central
venous pressure may reflect the loss of as much as
20% of the circulating blood volume. Likewise a
diminished arterial pulse contour (loss or migration
of the dicrotic notch) may identify hypovolemia that
would not be recognized by vital signs alone (53).
Metabolic acidosis secondary to hypoperfusion and
low or concentrated urine output are additional
indicators of hypovolemia. Proper assessment of
volume status aids interpretation of obtained hemo-
globin levels. A volume depleted child may have a
normal hemoglobin value. Once volume resuscita-
ted, however, a more realistic lower hemoglobin
level may reveal significant anemia.

Like adults, large amounts of blood may be lost
internally secondary to a long bone fracture, retro-
peritoneal bleeding or blunt abdominal trauma.
Unique to the child is the potential for substantial
bleeding from closed head trauma. Infants and
toddlers have open cranial sutures which allows
for collection of a substantial amount of intracranial
blood. Young pediatric patients may suffer from
hemorrhagic shock secondary to closed head injury, while older children and adults are unlikely to encounter this result.

Volume resuscitation should be initiated with large bore intravenous access. It may be difficult to access peripheral veins in a hypovolemic child. Short length, thin walled catheters have been successfully placed in the femoral or antecubital veins of dehydrated pediatric patients (54). The intraosseous route of fluid delivery may be life saving for delivery of fluids, medications, and dilute blood products when intravenous access cannot be obtained (55–57).

The efficacy of colloid administration instead of crystalloid has been debated for many years. Hypertonic saline and dextran solutions have been demonstrated to increase survival in hypotensive patients with severe head injury as well as patients with penetrating trauma when compared with standard resuscitation with normal saline (58, 59). However, no randomized controlled studies of pediatric patients have been published. In addition hypertonic saline/dextran solutions as well as hydroxyethyl starch are potential causes of coagulopathy in trauma patients (60). These solutions appear to compromise clotting by interfering with factor VIII as well as von Willebrand factor, resulting in a von Willebrand syndrome (61, 62).

The severely injured child may require massive blood transfusion. The metabolic consequences of massive transfusion including hypothermia, hyperkalemia, hypocalcemia, and hypomagnesemia are discussed in part I. Coagulopathy is also more likely to develop in a massively transfused child who has suffered from hypoperfusion or hypothermia (63). Although dilutional thrombocytopenia has been labeled as the primary reason for coagulopathy in the massively transfused patient, most studies demonstrating this point were carried out using whole blood (4, 64). Since most transfusion therapy, especially in the trauma patient, is now administered as packed RBCs, dilution of clotting factors may be an equally important cause of coagulopathy. In fact, the dilution of clotting factors has been demonstrated to become clinically important (with PT and PTT approaching 1.5–2 times normal levels) when 1.5 blood volumes have been transfused (Table 2) (65–67). On the other hand, platelet counts which begin as normal (>150 000 mm$^3$) are unlikely to be the cause of clinically significant coagulopathy until more than two blood volumes have been transfused (Figure 1) (1).

B. Neonates

Neonates pose some unique challenges with respect to anesthesia and blood products. One potential complication of RBC transfusion that occurs less frequently in neonates compared with older children and adults is a major hemolytic reaction. For the first 3–4 months of life, infants are unable to form alloantibodies to RBC antigens (68–70). After initial screening for ABO/Rh determination, repeated screening for antibodies is generally not necessary. With the exception of exposure to the Rh-D antigen, hemolytic reactions due to ABO incompatibility rarely occur in young infants because of their immature immune systems. Therefore, administration of RBCs to infants less than 4 months of age may be either type specific or O negative and do not require further cross matching. Beyond the first 4 months of life, hemolytic reactions remain an important cause of transfusion related morbidity and mortality.

Premature infants may be more susceptible to hypocalcemia hypothermia with large volume blood transfusions. As noted previously, transfusion-related graft versus host disease occurs more often in sick neonates and may require special consideration for the use of directed donor components from close relatives (pretransfusion irradiation) (69, 71, 72). Filtration to leukocyte-deplete blood products prior to transfusions should be routine in neonates and is likely to reduce the incidence of febrile nonhemolytic transfusion reactions, transmission of CMV infection, as well as transfusion-mediated immunomodulation.

C. Cardiac surgery

Children are prone to more hemostatic disturbances after cardiopulmonary bypass (CPB) than adults. Children with cyanotic congenital heart lesions are at high risk for hypoxemia and resulting polycythemia. Hypoxemia prolongs bleeding times by negatively affecting platelet function. Patients with congenital heart disease have also demonstrated a high incidence (19%) of abnormal preoperative PT and PTT values, as well as abnormalities in von
Willebrand factor (73, 74). Decreased clotting factor production may be caused by hepatic congestion secondary to heart failure. Disseminated intravascular coagulopathy may consume clotting proteins as well. Multiple factors, which may be identified preoperatively, contribute to these patients’ increased risk for perioperative bleeding.

Neonates are at highest risk for increased bleeding after cardiac surgery in part because of immaturity of the coagulation system (75, 76). In addition, many newborns undergo complex repairs that require longer cardiopulmonary bypass (CPB) times, deep hypothermia, or circulatory arrest, all of which have been demonstrated to result in increased perioperative bleeding (76–79); the risk of perioperative bleeding increases with decreasing patient age.

The relatively large volume of CPB pump prime significantly dilutes the small child’s clotting factor and platelet levels. Modern CPB pumps use much smaller volumes and are less likely to contribute to coagulopathy due to hemodilution (80). Ultrafiltration of the blood remaining in the CPB circuit helps to increase the patient’s hemoglobin as well as maintain high levels of clotting factors and platelet numbers (81, 82). Alternatively, intraoperative hemodilution by removing whole blood from the patient to be given after CPB as well as bloodless priming of the CPB pump have successfully limited patients’ exposure to homologous blood components after cardiac surgery (83–88). Prebypass removal of blood for later transfusion should preserve platelet function by eliminating the exposure of the platelets to the damaging effects of the bypass machine while also providing replacement of clotting factors. This technique is limited to larger pediatric patients. Intraoperative blood salvage (i.e. cell saver) may also be utilized in these patients, however, ultrafiltration yields higher levels of functional platelets and clotting factors (85–88).

Aprotinin, a serine protease inhibitor, prevents fibrinolysis and platelet activation normally seen after CPB (89–91). When given by high dose regimen, it decreases blood loss in pediatric cardiac patients undergoing complex surgery or resternotomy (92). In addition to its hemostatic benefits, aprotinin has also been linked to improved postoperative oxygenation resulting in less postoperative ventilation time (89). This may be attributed to its systemic anti-inflammatory effects. Some studies demonstrated no benefit of aprotinin in children (93), and raised concerns regarding allergic potential and renal impairment (94–96). However, other studies have found a low risk to benefit ratio and reduced cost with the use of high dose aprotinin in this pediatric surgical population (89, 92, 94, 97–99). The risk of allergic reaction upon secondary exposure to aprotinin in the pediatric population is less than half that of adults’ (1.2% vs. 2.7%) (100). To further lessen this incidence, the time between aprotinin exposures is recommended to be greater than 6 months (101). In high risk patients, a test dose of 10 000 KIU should be given when surgeons are prepared to initiate bypass quickly, and preemptive histamine blockade should be considered (101).

D. Tonsillectomy and adenoidectomy

Tonsillectomy is one of the most common pediatric surgical procedures. Although perioperative transfusion is rare, the procedure carries potential for life threatening hemorrhage. The majority of early bleeding episodes occur within the first 4–6 h after the procedure (102–105). Late bleeding typically occurs 5–10 days postoperatively (102–105). Late bleeding is commonly associated with an episode of early bleeding (104). In either situation, a significant amount of blood may be swallowed by the child, which makes assessment of its severity difficult. The child who is hypovolemic from decreased oral intake secondary to pain may have an artificially elevated hematocrit. Careful assessment of the patient’s volume status and laboratory values are imperative to a proper evaluation and preparation for reoperation. Blood pressure and heart rate determination in both the supine and sitting position may shed light upon the child’s intravascular volume status.

No universal practice of preoperative screening for increased risk of bleeding has been adopted by all otolaryngologists. Multiple studies have demonstrated that neither preoperative bleeding history nor routine laboratory screening with PT, PTT, and bleeding time are reliable predictors of postoperative bleeding (106–109). However, laboratory screening may be useful in patients who have a history suggestive of a major bleeding disorder. Even in these individuals, screening tests such as the PT and PTT may fail to identify some patients with bleeding
tendencies. The platelet function analyzer (PFA) is a relatively new tool which simulates primary hemostasis and is particularly well suited for evaluating suspected cases of von Willebrand’s disease or intrinsic platelet defects (110, 111). More formal consultation with a hematologist is strongly recommended to determine the most appropriate course of preparation for surgery. For example, patients with the most common type of von Willebrand disease can undergo successful, nonhemorrhagic adenotonsillar surgery if treated appropriately with DDAVP [desmopressin (1-deamino-8-D-arginine vasopressin)]. Other subtypes, however require the use of cryoprecipitate or plasma-derived factor VIII concentrate containing von Willebrand factor (112). Bleeding in patients with intrinsic platelet defects can be prevented or controlled with platelet transfusions. Without proper family and patient history and subsequent testing, these patients may not be identified preoperatively and may suffer from marked, uncontrollable bleeding. It appears that meticulous surgical technique is the most important factor assuring that postoperative hemostasis is maintained regardless of the patient’s history.

The use of ketorolac for postoperative pain control in tonsillectomy patients has been debated in the literature. Although an effective analgesic, concerns regarding its antiplatelet activity have limited its use. Several studies have demonstrated increased perioperative bleeding associated with ketorolac use for analgesia following tonsillectomy, however, none identify the need for further intervention in these patients (113–117). Ketorolac has been demonstrated to lower pain scores when compared with placebo (118). It is unclear whether or not ketorolac use changes clinical outcome in the pediatric adenotonsillar surgery population. However, because of its theoretical risk of inhibiting platelet function, it is prudent to reserve its use until after the surgery has been completed and hemostasis obtained. After initial hemostasis has been obtained, the influence of platelet function upon subsequent hemorrhage should be less (119). The next generation of cox-2 inhibitors will not have this antiplatelet effect and should provide analgesia without respiratory depression or the potential for bleeding. However, other methods of pain control have been shown to be equally efficacious without the potential risk for increased bleeding (114, 115, 117).

E. Orthopedics

The vast majority of pediatric orthopedic procedures are accomplished without the need for blood transfusions. However, the inability to use a surgical tourniquet (such as femoral osteotomy or spinal fusion cases) can result in clinically important blood loss. The incidence and severity of the blood loss is often dependent upon the skills of the surgeon. A number of techniques such as hemodilution and controlled hypotension have been advocated to reduce the exposure to exogenous blood products, however concerns for impaired spinal cord blood flow during spinal instrumentation have altered our practice. We no longer advocate combined controlled hypotension and extreme hemodilution. If we reduce blood pressure it is only reduced to a modest range (mean arterial pressure 65–75 mmHg) and we generally do not allow the hemoglobin to fall below 8 g dL\(^{-1}\). If the patient develops abnormal bleeding in an early part of the procedure it is vital to check the patient’s position to assure that the support bolsters have not changed position resulting in increased intraabdominal pressure thereby increasing venous pressure by mechanical obstruction.

One further concern is that after major spine fusion procedures there may be the potential for continued bleeding from the raw surfaces of bone; therefore, it is our practice to transfuse these patients so that their hemoglobin at the end of surgery is in the 10–11 g dL\(^{-1}\) range. The use of aprotinin, epsilonaminocaproic acid, tranexamic acid, or DDAVP has failed to consistently demonstrate decreased blood loss (120).

F. Neurosurgery

One study has demonstrated that pediatric patients undergoing neurosurgical procedures may have a hypercoagulable state postoperatively as demonstrated by TEG (121). However, the primary cause of problems related to hemostasis in neurosurgical procedures are attributable to massive blood loss and subsequent dilutional coagulopathy or disseminated intravascular coagulopathy (DIC). Neural tissue injury due to trauma can also result in tissue thromboplastin release and subsequent activation of the coagulation cascade via FVIIa. Children
undergoing resection of vascular malformations and vascular tumors (e.g. choroid plexus adenoma) as well as trauma patients with epidural or subdural hematomas are at great risk for massive and rapid blood loss. Children with traumatic brain injury and shaken baby syndrome are at particular risk for the development of DIC. In each of these cases it is prudent for the clinician to use invasive monitoring (arterial and central venous monitoring) as well as large bore intravenous catheters with appropriate blood warming devices (see part I). It is rare for children undergoing elective resection of brain tumor to develop a coagulopathy unless it is due to dilution of clotting factors.

G. Burns

Children with burn injuries can develop a variety of clotting factor abnormalities. These abnormalities depend in part upon the extent of the burn injury, the presence or absence of sepsis, and the volume of blood shed during reconstructive surgery. Early after massive burn injury there is both a consumptive coagulopathy and a microangiopathic hemolytic process (122, 123). Thus anemia, thrombocytopenia, and evidence of coagulopathy are common. After the initial 3–5 days following burn injury the typical anti-inflammatory response occurs and patients develop marked increases in fibrinogen, platelets, as well as a variety of clotting factors (122–124). Platelet counts over 1000 000 mm$^{-3}$ and fibrinogen values over 2 g dl$^{-1}$ may be observed. Despite these abnormalities it is rare for pediatric burn victims to suffer thrombotic events. Conversely with the onset of sepsis there may be a sudden fall in the platelet count. Excision of burn wounds can also involve rapid and massive blood loss; some of this blood loss may be reduced by using saline with dilute concentrations of epinephrine injected under both the donor and recipient sites (clysis) (125). In addition, because the skin has been damaged it no longer provides the normal insulation to the body such that these patients are particularly prone to hypothermia. Thus, although uncomfortable, it is wise to use a very warm operating room (35°C). The administration of blood products should be guided by serial platelet counts and evaluation of the PT and PTT (66). In general, abnormal bleeding does not occur if the platelet count is maintained above 50 000 mm$^{-3}$ (1). It should also be kept in mind that central venous lines, especially those with multiple ports, will be inadequate to rapidly administer RBCs since there is so much resistance (126). Short-term femoral venous catheterization for the procedure with a large bore short catheter provides a better means for rapid RBC transfusion.

H. Kidney transplantation

Patients with renal failure have anemia for multiple reasons. As kidney failure progresses, erythropoietin production decreases, red blood cell life span shortens secondary to hemolysis from circulating toxins, and iron and folic acid deficiencies ensue (127). In addition, hemodialysis increases the severity of anemia secondary to chronic blood loss within the dialysis circuit and progressive reduction in erythropoietin levels compared with peritoneal dialysis (128). Nevertheless, this anemia (typical hematocrit 25%) is chronic, and therefore, generally well tolerated if the patient is euvolemic. The threshold for preoperative transfusion of these patients should be lower than for the general population in whom perioperative anemia is more likely to be acute and less well tolerated. Historically, blood transfusion was performed pretransplant for the purpose of inducing immunosuppression. With the advent of more controlled medical immunosuppressive therapy (e.g. cyclosporin), the practice of automatic pretransplant transfusion of these patients has mostly fallen out of favor. In fact, there is some evidence that blood transfusion to pediatric transplant recipients may actually be contributory to the increased incidence of rejection in this population (129). Alternatively, recombinant erythropoietin [Epogen® (rhEPO), Amgen, Inc., Thousand Oaks, CA, USA] has successfully increased hemoglobin levels of pediatric renal failure patients over a period of a few months (128). Erythropoietin therapy may aid in increasing the patient’s oxygen carrying capacity if begun enough in advance of a planned renal transplant (e.g. a living donor).

Patients with renal failure are at increased risk for platelet dysfunction secondary to uremia thereby increasing bleeding tendencies. Although thrombocytopenia is not uncommon, platelet dysfunction appears to be more problematic. There are multiple causes of platelet dysfunction in this population,
some of which can be at least partially treated with dialysis (130, 131). Platelet transfusion as well as DDAVP may be helpful in the patient with a continued prolonged bleeding time despite dialysis (132).

Pediatric renal transplants differ from those of adults intraoperatively secondary to size discrepancies between donor organ and recipient. It is common for small pediatric patients to receive a kidney from an adult donor. In this situation, it is possible for a large amount of blood (150–250 ml) to be sequestered into the organ upon vascular unclamping. This may be a significant portion of the pediatric recipient’s blood volume and may result in hypovolemia and hypotension upon reperfusion. Central venous pressure monitoring is helpful in anticipation of this problem and also because urine output is an unreliable indicator of volume status in these patients. In some circumstances a unit of packed RBCs is administered prior to reperfusion of the donor kidney.

I. Liver transplantation

Pediatric liver transplant patients are often anemic. Chronic disease, nutritional deficiencies, and occult blood loss contribute to decreased hemoglobin levels. These patients are typically coagulopathic for a variety of reasons including but not limited to hypersplenism and decreased clotting factor production. Malabsorption of vitamin K leads to decreased production of vitamin K-dependent factors II, VII, IX and X resulting in elevated PT and PTT. Thrombocytopenia may be the result of splenic sequestration secondary to portal hypertension, DIC, or dilution from increased plasma volume. Although preoperative coagulation tests have not been shown to correlate with intraoperative blood loss during pediatric liver transplantation, they are important indicators of the severity of liver disease and help to establish a baseline to which intraoperative values can be compared (133, 134). Hemoglobin levels, platelet numbers, PT and PTT values and whole blood clotting assays such as the thromboelastogram (TEG) are used to guide perioperative blood product administration.

Pediatric liver transplant patients are at even higher risk than adults for requiring massive transfusion. Infants have demonstrated increased transfusion needs during liver transplant than older children and adults (135). Previous abdominal surgery has been linked to increased blood use during liver transplantation (134). The most common etiology of pediatric liver failure is biliary atresia for which previous abdominal surgery (i.e. Kasai portoenterostomy), is often performed prior to transplant. The use of reduced-sized donor livers is common in children because they often receive a lobe or segment of a living related donor organ, or a split cadaver organ which can serve two patients. The use of reduced sized grafts has also been associated with increased intraoperative bleeding (136).

Adequate venous access is critical for these patients. Large bore intravenous lines should be placed in the upper extremities because the inferior vena cava may be cross-clamped intraoperatively. If adequate access in the upper extremities is not possible, large bore access may be placed via the subclavian or jugular veins. Great care must be taken when inserting large central venous cannulas in the neck region if coagulopathy exists as hematoma formation may be difficult to control. Ultrasound guided catheter insertion may be very advantageous in this population (137, 138). The hospital blood bank must have well-organized and well-equipped resources to handle the potential massive transfusion needs of these patients (multiple blood volumes). Our blood bank defines massive blood transfusion according to Table 4. For this population, our practice is to have one blood volume of cross-matched packed RBCs, five to 15 units of fresh frozen plasma and two to four plasma pheresis packs of platelets. After one blood volume of blood

<table>
<thead>
<tr>
<th>Patient weight (kg)</th>
<th>Packed red blood cell units transfused per 24 h</th>
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<tbody>
<tr>
<td>0.5–7</td>
<td>2</td>
</tr>
<tr>
<td>7–15</td>
<td>3</td>
</tr>
<tr>
<td>16–20</td>
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<td>41–50</td>
<td>9</td>
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<td>&gt;50</td>
<td>10</td>
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Table 4

Units of crossed matched blood transfused within 24 h after which cross-match is no longer required and type specific red blood cells may be utilized.
transfusion a cross-match is not required and type specific packed RBCs are used. The anesthesiologist must be prepared for complications of massive blood transfusion including hypothermia, hypocalcemia, hypomagnesemia, and hyperkalemia. Citrate induced hypocalcemia is a particular problem in these patients because of decreased ability to metabolize citrate secondary to liver failure and the inability to metabolize citrate during the anhepatic stage of the transplantation. If rapid and massive transfusion is expected, a calcium chloride infusion may be prudent to avoid hemodynamic instability caused by rapidly changing ionized calcium levels.

V: Reduction of allogeneic blood administration

There are multiple methods aimed at reducing perioperative homologous blood administration (139, 140). For planned surgery in which blood transfusion is expected (e.g. scoliosis repair), the possibilities of autologous blood donation, erythropoietin therapy, and cell salvage should be considered. Autologous blood donation involves the removal of the patient’s blood a week or more prior to surgery. This blood is then treated and processed by a blood bank center and is released for that specific patient’s use on the day of surgery. This process theoretically limits the likelihood of transfusion related infectious disease (except bacterial) and decreases the incidence of incompatibility issues. The unit must be cross-matched to a fresh sample of the patient’s blood prior to release. However, clerical error in processing, labeling, testing, and final checking of the unit is still possible, and thus administration of what is deemed an autologous unit is not without risk. In addition, the metabolic consequences of transfusion of autologous blood are the same as with allogeneic transfusion. Autologous blood is often stored as whole blood and will thus contain all clotting factors in normal concentrations except labile factors V and VIII. Whole blood will also carry an increased risk for hyperkalemia and/or hypocalcemia if older than 7 days and rapidly administered. The hematocrit will be lower than packed RBCs. Autologous donation has successfully decreased allogeneic blood transfusion for children 8–25 kg undergoing orthopedic or abdominal procedures (141).

An alternative method of autologous blood use without predonation through a blood bank is acute normovolemic hemodilution (ANH) at the beginning of surgery and prior to the onset of surgical blood loss. With this method, blood is removed from the patient (usually from an arterial line) and collected into appropriate storage bags (placed on a scale to quantify the volume removed). Careful replacement of the removed blood volume with crystalloid in a 3 : 1 ratio is important in order to maintain normovolemia. The amount of blood to be removed should be precalculated and the collection bag weighed in order to avoid withdrawal of too much blood. This is important when caring for small children because one must think in the terms of milliliters of blood instead of units of blood. The anesthesiologist must also be careful not to overfill the storage bag. The storage bags contain a specified amount of citrate as an anticoagulant for 450 ml of whole blood. If the bag is overfilled, there may be insufficient anticoagulant to prevent thrombus formation. After removal of this blood, the patient then sheds intraoperative blood with a lower hematocrit (i.e. fewer RBCs per plasma volume lost to surgery) and the autologous blood can be administered after the majority of blood loss has been completed. The use of ANH has been shown to effectively decrease the need for allogeneic blood transfusion in adolescent spine surgery (142). If the removed autologous unit remains in the operating room (preferably in a cooler to reduce RBC metabolism and the potential for bacterial growth), the likelihood of clerical error and incompatibility is minimized, however the metabolic consequences of transfusion still exist.

Preoperative administration of erythropoietin has been used to increase hemoglobin levels and reduce the need for intraoperative or postoperative transfusion (143). Many studies demonstrating the efficacy of erythropoietin have involved adults undergoing orthopedic procedures (144–146). Erythropoietin may also be used in combination with autologous blood donation to further reduce the need for allogeneic blood exposure. One small study involving children undergoing open heart procedures was successful in eliminating allogeneic blood exposure through a combination of autologous predonation and erythropoietin therapy over a period of 2 weeks (147).
Intraoperative cell salvage allows surgical blood loss to be collected, washed, and hemoconcentrated in preparation for autologous donation. The qualities of cell salvaged blood include an average hematocrit of 50%, normal erythrocyte survival, and minimal functional platelets (148). Contraindications for the use of this technique include surgical field contamination with bacteria, amnionic fluid, fat, or other potential clotting agents such as topical thrombin (149). Originally, cancer was a contraindication to intraoperative blood salvage for fear of bloodborne tumor spread however an analysis of six studies in which cell salvage was used for cancer patients revealed no metastatic spread (150). Also, the use of a leucocyte filter further reduces this risk (150). There are no firm guidelines in the literature for minimal expected cell salvage in order for cell salvage to be considered cost effective. In our institution, we consider cell salvage for liver transplant or scoliosis correction patients over 30 kg.

Conclusions

Surgeons are now much more meticulous in maintaining hemostasis in part because their patients demand this and anesthesiologists are much more circumspect with regard to transfusions thereby minimizing our patient’s exposure to blood products. These papers were intended to present a clinically oriented overview of perioperative blood transfusion practices. Our purpose was to present the topic in an easily understood format with a generous use of tables and figures. We hope that we provided useful strategies for a logical approach to transfusion therapy and the associated complications as well as insight into the most recent understanding of the coagulation cascade and innovations in recombinant clotting factor replacement. From our viewpoint the most important issue is that the blood pool is becoming increasingly safe through better screening. The future is even more exciting with the development of artificial blood, additional recombinant clotting factors, and new medications that further improve coagulation thereby further reducing exposure to allogenic blood products. Our hope is that blood banks and health care systems around the world will have the resources to take advantage of these wonderful innovations.

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