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Hyperleukocytosis in infant acute leukemia: a role for manual exchange transfusion for leukoreduction

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Abstract

BACKGROUND—Hyperleukocytosis is a serious, life-threatening complication of pediatric acute leukemia that can cause neurologic injury, pulmonary leukostasis, metabolic derangements, and coagulopathy. Acute leukemia has the highest risk of mortality and morbidity at presentation when associated with hyperleukocytosis. Infant leukemia presents unique challenges and treatment considerations due to the disease itself and size and overall health of the patient. While medical management of hyperleukocytosis in older patients with acute leukemia has been described, including cytoreductive procedures with automated leukapheresis (AL) or manual whole blood (WB) exchange transfusion, very little data exist for standardized management of hyperleukocytosis in infant leukemia patients.

CASE REPORTS—We describe four cases of infant acute leukemia presenting with hyperleukocytosis and leukostasis who each received manual WB exchange transfusions in conjunction with induction chemotherapy and review the existing literature on the use of procedural leukoreduction in infants with hyperleukocytosis. Special attention is given to challenges and technical aspects of leukapheresis in infants: when to perform manual WB exchange versus AL, optimal vascular access, blood product selection, exchange rates, and the monitoring for complications. Using published cases, we outline benefits versus risks of manual WB exchange and AL in infants less than 10 kg.

CONCLUSION—If providers perform procedural leukoreduction, the literature and our experience demonstrate manual WB exchange transfusion is favored over AL in infants less than 10 kg because of technical and complication risks associated with AL. Additional studies are needed to understand the impact of cytoreduction on long-term outcomes.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

Hyperleukocytosis is a potential complication of acute leukemia occurring more frequently at presentation for infants compared to non-infant childhood acute leukemia. Resultant leukostasis causing respiratory failure, stroke, and organomegaly in conjunction with tumor lysis syndrome underlie the early high risk of morbidity and mortality in this population. Approximately 5% to 20% of new diagnoses of acute leukemia in pediatric patients present with hyperleukocytosis,¹ but there are limited data specifically for infant leukemia, which requires providers to rely on expert recommendation for older children and adults.^{2–4} Conservative management with hydration, initiation of chemotherapy and other cytoreductive agents such as steroids or hydroxyurea, and electrolyte management has been shown to be immediately beneficial and crucial, with no added benefit of delaying chemotherapy for leukapheresis.^{2,3,5,6} However, in the setting of any of these early complications, hyperleukocytosis may necessitate additional aggressive and urgent intervention to achieve cytoreduction, which should include medical management and/or procedural cytoreduction.^{7–10} While the importance of early identification and intervention with symptomatic hyperleukocytosis has been established, the use of apheresis in hyperleukocytosis remains extremely controversial and there has not been evidence that the procedure improves short- or long-term survival.^{11–13}

Although manual whole blood (WB) exchange is commonly performed in newborns with severe hyperbilirubinemia from hemolytic disease of the newborn due to their small size (<5 kg),¹⁴ clinical experience with performing this procedure for infants with leukemia and hyperleukocytosis is lacking and primarily limited to case reports with varying levels of details on the procedures themselves. While guidelines are available that outline appropriate scenarios for automated leukapheresis (AL) in older children and adults with leukemia and hyperleukocytosis, they provide no recommendations on when and how to perform manual WB exchange for infant leukemia.⁴ We discuss four infants with newly diagnosed leukemia and symptomatic leukostasis syndrome successfully treated with manual WB exchange at our institution. The cases are also summarized in Table 1. Additionally, we provide an overview of the existing literature regarding the use of manual WB exchange and AL procedures in infants with hyperleukocytosis. Finally, we outline our recommendations for the use of cytoreduction in infants with leukemia in conjunction with other acute leukemia therapies.

CASE REPORTS

Patient 1 was a previously healthy 6-month-old, O1 male, weighing 8.9 kg who presented with dyspnea, fatigue, red-purple lesions (chloromas) on the scalp, and hepatosplenomegaly. Chest radiograph demonstrated pulmonary edema and abdominal ultrasound showed nephromegaly and hepatosplenomegaly consistent with leukemic infiltration. He was diagnosed with infant acute lymphoblastic leukemia and initial laboratories revealed a white blood cell (WBC) count of $423 \times 10^9/\text{L}$ (95% lymphoblasts), hemoglobin (Hb) level of 8.1 g/dL, platelet (PLT) count of $53 \times 10^9/\text{L}$, lactate dehydrogenase (LDH) level of 2390 U/L, and uric acid level of 6.8 mg/dL. There was no evidence of coagulopathy, electrolyte abnormalities, or organ dysfunction. A double-volume manual WB exchange was performed over 9 hours using 1120 mL ($75 \text{ mL/kg} \times 8.9 \text{ kg} \times 2$) of reconstituted WB (group O– non–volume-reduced red blood cells [RBCs] and group AB plasma with hematocrit [Hct] of

24%) as replacement. The exchange transfusion was performed with reconstituted WB infusing at 13.5 mL/kg/hr (120 mL/hr) on an infusion pump through an internal jugular double-lumen central venous line (CVL). Every 15 minutes, 30 mL (3.4 mL/kg) of WB was withdrawn from a radial arterial line. Methylprednisolone and rasburicase were administered before exchange transfusion. Immediately after the procedure, the WBC count decreased to $49 \times 10^9/L$ (89% lymphoblasts), with a Hb level of 7.2 g/dL and PLT count of $33 \times 10^9/L$. The procedure was well tolerated without immediate complications.

Patient 2 was a previously healthy 5-month-old, B– male, weighing 7.0 kg, who presented with fever, dyspnea, bruising, pallor, and hepatosplenomegaly. He was diagnosed with infant acute lymphoblastic leukemia and initial laboratories revealed a WBC count of $890 \times 10^9/L$ (98% lymphoblasts), Hb level of 4.8 g/dL, PLT count of $10 \times 10^9/L$, LDH level of 1725 U/L, and uric acid level of 9.8 mg/dL. There was no evidence of coagulopathy, electrolyte abnormalities, or organ dysfunction. RBC and PLT transfusion was administered before CVL placement. A double-volume WB manual exchange transfusion was performed using 1200 mL ($85 \text{ mL/kg} \times 7 \text{ kg} \times 2$) of reconstituted WB (B– non–volume-reduced RBCs and group B plasma reconstituted to Hct of 30%) as replacement. The exchange transfusion was performed over 2 hours with the product infusing at approximately 85 mL/kg/hr through peripheral intravenous (PIV) line and withdrawing the same volume in 10- to 20-mL increments from a double-lumen femoral CVL. The patient was started on prednisone 1 day before the procedure and received rasburicase before exchange. After the procedure, the WBC count decreased to $434 \times 10^9/L$ (96% lymphoblasts), with a Hb level of 7.5 g/dL and PLT count of $127 \times 10^9/L$ (after PLT transfusion). The patient tolerated the procedure well with no immediate complications.

Patient 3 was a previously healthy 3-month-old, O+ female weighing 4.65 kg, who presented with respiratory distress, pallor, and hepatosplenomegaly. She was diagnosed with infant acute lymphoblastic leukemia and initial laboratories demonstrated a WBC count of $1119.8 \times 10^9/L$ (82% mixed lymphoblasts and myeloblasts), Hb level of 5.4 g/dL, PLT count of $20 \times 10^9/L$, LDH level of 8875 U/L, and uric acid level of 8.4 mg/dL. There was no evidence of coagulopathy, electrolyte abnormalities, or other organ dysfunction. A single-volume WB manual exchange transfusion (400 mL; $86 \text{ mL/kg} \times 4.65 \text{ kg}$) was performed followed by a double-volume WB manual exchange transfusion (864 mL; $90 \text{ mL/kg} \times 4.65 \text{ kg} \times 2$) due to persistent hyperleukocytosis, respiratory failure, and laboratory abnormalities. The WBC count decreased to $738.9 \times 10^9/L$ (94% mixed lymphoblasts and myeloblasts) after first exchange with a Hb level of 9.2 g/dL and a PLT count of $63 \times 10^9/L$. After the second exchange, the WBC count was $270.38 \times 10^9/L$ (87% mixed lymphoblasts and myeloblasts) with a Hb level of 13.8 g/dL and a PLT count of $64 \times 10^9/L$. The replacement product was O – RBCs and group AB plasma reconstituted to Hct level of 40%. The details of the duration of the procedure and infusion rate were not available. Hydroxyurea was started before the manual WB exchanges. RBC (5 mL/kg) and PLT (10 mL/kg) transfusions were given before line placement (double-lumen CVL and arterial line). The procedures were well tolerated without any immediate complications.

Patient 4 was a previously healthy 10-week-old, O+ male weighing 4.7 kg who presented with respiratory failure and abdominal distention. He was diagnosed with infant acute

lymphoblastic leukemia. Initial laboratories demonstrated a WBC count of $260.71 \times 10^9/L$ (74% mixed lymphoblasts and myeloblasts), a Hb level of 6.6 g/dL, a PLT count of $41 \times 10^9/L$, LDH level of 3519 U/L, and uric acid level of 17.3 mg/dL. The patient had electrolyte abnormalities including hyperkalemia and hyperphosphatemia as well as significant coagulopathy (prothrombin time of 52.5 sec, partial thromboplastin time of 49.0 sec, and fibrinogen level of <100 mg/dL). In addition to disseminated intravascular coagulation, the patient was found to be in septic shock. The patient was immediately started on allopurinol and methylprednisolone and received one dose of rasburicase. The patient was intubated due to pulmonary leukostasis and a double-volume manual WB exchange transfusion (948 mL; $100 \text{ mL} \times 4.7 \text{ kg} \times 2$) was performed over 4 hours at approximately 40 mL/kg/hr. Reconstituted WB using group O– RBCs and group AB plasma (Hct level of 25%) was infused via PIV with WB removal from an arterial line. After the procedure, WBC count was $52.76 \times 10^9/L$ (90% mixed lymphoblasts and myeloblasts), with a Hb level of 6.3 g/dL and a PLT count of $34 \times 10^9/L$ (after PLT transfusion). The patient then received a PLT transfusion before central line placement. The procedure was well tolerated without any immediate complications.

DISCUSSION

We describe four cases of infant acute leukemia with symptomatic hyperleukocytosis in which manual WB exchange transfusion was safely and efficiently implemented. However, there currently are no specific recommendations on the preferred cytoreduction procedure in this group of patients due to the relative dearth of experiences documented in the medical literature. The available literature is limited to a few case reports^{5,7–9,15–19} and fails to adequately address questions that arise when performing leukapheresis in infants, such as when to perform manual WB exchange versus AL, optimal vascular access to be utilized, blood product selection, exchange (infusion/removal) rates, and the monitoring for complications. Highlighting our cases and those in the literature, if procedural cytoreduction is being performed, we recommend the use of manual WB exchange for infants weighing less than 10 kg with acute leukemia presenting with symptomatic hyperleukocytosis. Table 2 outlines previously reported case studies in the literature. As demonstrated in the table, numerous and significant gaps exist in outlining the specific procedures for executing a manual WB exchange transfusion. Where data do exist, there is considerable variability on the volumes exchanged, rates of infusion and withdrawal, vascular access, and method used (automated vs. manual).

A single AL can reduce total WBC count by 30% to 60% depending on the processed blood volumes and technical procedural modulations (i.e., collection flow rate), but manual double-volume WB exchange can remove up to 85% of blasts from the periphery.⁴ Since chemotherapy is often given concurrently, it can be difficult to ascertain the direct impact of WB exchange or AL on the WBC decrease. Once the decision is made to perform a cytoreductive procedure, clinicians should consider the availability of a trained apheresis team experienced with the procedure in small patients. In centers without trained on-call apheresis teams comfortable with small patients, leukoreduction via manual WB exchange should proceed in consultation with critical care and transfusion services trained in this procedure for treating hemolytic disease of the newborn.²⁰

Patient weight, the presence of coagulopathy including thrombocytopenia, and risk for other metabolic or organ dysfunction are additional factors to consider in deciding to proceed with manual versus automated exchange. The most important consideration is the weight of the infant. The technical requirements of blood cell separators which are designed for adults make therapeutic apheresis procedures more challenging in young children, especially those under 10 kg. In addition to the need for blood primes for children less than 20 kg, the necessary blood flow rates for blood cell separation (usually > 15 mL/min) are often difficult to maintain in very young children due to the small caliber of their venous access and their particular vulnerability to citrate toxicity at the flow rates required to maintain CVL patency. As an example, to maintain an inlet flow rate (15 mL/min) using citrate only for anticoagulation in a 7-kg infant receiving AL (assuming a WB-to-anticoagulant [AC] ratio of 12:1), the patient would receive an AC infusion rate in excess of 2.1 mL/min/L total blood volume, which would place the patient at significant risk for citrate toxicity despite intravenous (IV) calcium supplementation. To minimize this risk, some centers have adopted combined citrate/heparin anticoagulation protocols (e.g., adding 10 units heparin/mL ACDA-1 and infusing at WB-to-AC ratio of 30:1) to reduce the risk of citrate toxicity during leukapheresis procedures.²¹ However, heparin-induced bleeding risks need to be carefully assessed and monitored in infants with acute leukemia who may have an existing coagulopathy due to their disease process.

Unlike other therapeutic apheresis procedures (i.e., plasmapheresis), AL results in a significant net volume and RBC loss.²¹ As such, careful fluid balance monitoring is critical to compensate for predicted losses and maintain euvolemia. Furthermore, since the removed product bag includes WBCs, PLTs, plasma, and RBCs (with a Hct level of up to 7%), multiple blood products may be necessary to replace coagulation factors, PLTs, and RBCs lost during large or repeated leukapheresis procedures to minimize risk of hemorrhage and worsening anemia. Additionally, due to the slow inlet flow rates required in small infants on AL (15 mL/min), the time to establish the interface, which is necessary before cytoreduction, may take up to 90 minutes, resulting in long procedure times. Based on these considerations, AL is usually not recommended for children weighing less than 10 kg²¹ unless combined citrate/heparin anticoagulation protocols are utilized. Finally, AL puts patients at high risk for hypocalcemia. Most apheresis teams have established guidelines on electrolyte monitoring. Given the added possibility of hypocalcemia and other electrolyte derangements with tumor lysis syndrome, frequent monitoring is recommended.

For AL in children with body weight less than 20 kg, a blood prime (reconstituted to Hct of the patient) and a hemodialysis-grade CVL is universally indicated. Although either manual WB exchange or AL can be performed using a temporary dual-lumen high-flow CVL, manual WB exchange allows for additional vascular access options for the infusion and removal lines since the rate and pressure are manually controlled. As illustrated in our cases, an isovolumetric exchange can be performed through simultaneous infusion of reconstituted WB (RBC/fresh-frozen plasma [FFP] to Hct of the patient) and removal of the infant's leukemia-rich blood. Alternatively, one can perform a manual WB exchange using one central venous access point by employing a push-pull technique. Although no standard timeline exists on the appropriate amount of time to complete a WB exchange, it is generally recommended to not exceed an infusion/removal rate of 3 mL/kg/min (for isovolumetric

exchange technique) or 5 mL/kg over a 2- to 4-minute cycle (for push-pull technique).²² Table 2 shows the scant details outlining infusion and removal rate. However, it has been demonstrated both in our cases and in the published case studies that the manual WB exchange procedure can be safely completed in as little as 2 hours. The size of the patient and volume exchanged obviously affects these factors.

Although manual WB exchange does not require special apheresis equipment and staff, and is applicable in children with a body weight below 10 kg, many pediatric oncologists and nonneonatal critical care staff are not adequately trained in this procedure. Because this procedure replaces the patient's leukemia-rich WB with reconstituted WB at a 1:1 manner, the patient remains euvoletic, the anemia is not exacerbated, and metabolic abnormalities may be corrected due the replacement of the patient's plasma volume. It is important to monitor PLTs given the replacement product contains RBCs and FFP, but does not contain PLTs. While central line placement is deemed safe in pediatric patients with acute leukemia, literature and professional guidelines recommend placement with a PLT count of at least $20 \times 10^9/L$ if possible.^{23,24} PLT transfusion can generally be safely performed without increased risk of thrombotic injury in the setting of hyperleukocytosis, specifically due to the risk of intracranial hemorrhage in infant acute leukemia patients. RBC transfusions and high Hb concentrations are thought to precipitate leukostasis in patients with hyperleukocytosis, thus deferring simple RBC transfusion is preferred to avoid associated morbidity and mortality.^{1,5,25} If it is felt RBC transfusion cannot be delayed, it should be administered slowly with careful attention to fluid balance.¹³

Whereas IV calcium replacement is almost universally recommended for AL in children, it is often not necessary for manual WB exchange. Monitoring for hypocalcemia is recommended since citrate exposure occurs as a result of the reconstituted WB unit infusion. Because the guidelines for WB manual exchange transfusion are lacking, monitoring was not done in a standardized manner in our patients. However, it should be noted that none developed hypocalcemia. Additionally, electrolytes should be monitored after and possibly during the procedure depending on the clinical status of the patient and duration of the exchange transfusion. Clinicians should also consider the impact of concurrent chemotherapy and its effect on expected changes in electrolytes. Specifically, steroids cause tumor lysis and hydroxyurea can interfere with point of care glucose and creatinine monitoring.²⁶ Finally, while no specific guidelines exist on the administration of rasburicase before or after exchange transfusion, in patients with hyperleukocytosis, hyperuricemia, and/or tumor lysis syndrome, it is recommended that rasburicase be administered immediately.

For manual WB exchange, double-volume exchange is preferred over single-volume exchange to optimize blast removal. Assuming a total blood volume for infants of 75 to 85 mL/kg, a volume of 150 to 170 mL/kg is required. Our center prefers the use of fresh (<7 days) leukoreduced, irradiated, ABO/D group-specific or group-compatible for RBCs and plasma reconstituted to a final Hct equivalent to the Hct of the infant ($\pm 3\%$) to minimize the risk of hyperviscosity with hyperleukocytosis. If O, D- with group AB plasma is chosen, this will ensure universal compatibility, regardless of the infant's blood group, and can prevent unnecessary delays if a group type is unavailable. Alternatively, the use of ABO-

identical WB, if available and less than 14 days old, could be considered to decrease the risk of thrombocytopenia and reduce donor exposures.²⁷

Once the hyperleukocytosis is corrected, the patient can more safely receive simple transfusion of RBCs to correct the ongoing anemia. Thrombocytopenia should be carefully monitored as replacement products do not contain PLTs and intracranial hemorrhage is independently associated with thrombocytopenia. Given that these patients are often coagulopathic as well, a low threshold should be maintained for screening head imaging if indicated. Depending on the volume status of the patient, small aliquots can be transfused before vascular access without risk of hyperviscosity associated with RBC transfusion. Although early cytoreduction via either manual WB exchange or AL in conjunction with standard therapy can be beneficial toward rapidly reversing leukostasis syndrome²² and preventing or treating tumor lysis syndrome, the decision to perform WB exchange or AL should not delay other therapies including hydration, steroids or hydroxyurea, or initiation of definitive leukemia treatment.

In conclusion, the evidence for leukapheresis in infants with acute leukemia and hyperleukocytosis remains controversial with no specific recommendations or guidance on performing manual WB exchange versus AL versus no procedural leukoreduction. Existing literature fails to adequately identify the necessary technical details involved in the cytoreductive procedures or their effect on long-term survival. These four cases represent our center's most recent experience with manual WB exchange and demonstrate that it can be safe and effective for cytoreduction in infant leukemia patients with hyperleukocytosis and documented evidence of leukostasis injury including stroke, respiratory failure, or acute kidney injury. A summary of this outline is included in Fig. 1. When procedural cytoreduction is being performed, we recommend the use of AL for infants weighing more than 10 kg where a trained apheresis team exists and manual WB exchange for infants weighing less than 10 kg unless combined citrate/heparin anticoagulation protocols are utilized by adequately trained staff. However, a procedural cytoreduction should be performed in conjunction with other therapeutic measures to reduce risk of leukostasis (chemotherapy and hyperhydration).

While two of the four patients in this series ultimately died, each death occurred outside the immediate diagnosis period and were not due to complications of hyperleukocytosis, rather from the underlying disease process itself. This review underscores the need to further investigate hyperleukocytosis in infant leukemia as a unique disease process with specific attention given toward standardizing procedures for leukoreduction in infant leukemia patients.

ABBREVIATIONS

AC	anticoagulant
AL	automated leukapheresis
CVL	central venous line

PIV	peripheral intravenous (line)
WB	whole blood

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Fig. 1.

Decision tree for leukocytoreduction in acute infant leukemia with hyperleukocytosis and leukostasis. #Combined heparin/citrate anticoagulation protocols are recommended for AL patients less than 10 kg. NICU = neonatal intensive care unit.

TABLE 1

Summary of institutional manual WB exchange transfusions performed

Age (months)	Weight (kg)/sex	ABO/D	Dx	Volume	Infusion rate	Access	Blood product	Laboratory values	Details and outcomes
6	8.90/male	O–	B-ALL	75 mL/kg × 2	13.5mL/kg/hr	CVL PIV	O– RBCs AB plasma Hct 24%	WBC count ($\times 10^9/L$) Initial, 423 Post- WBEx, 49 Hb (g/dL) Pre-WBEx, 8.1 Post-WBEx, 7.2 PLT count ($\times 10^9/L$) Pre-WBEx, 53 Post-WBEx, 33	No immediate complications; no transfusions administered before line placement; no electrolyte abnormalities or coagulopathy.
5	7.00/male	B–	B-ALL	85 mL/kg × 2	85mL/kg/hr	CVL PIV	B– RBCs B plasma Hct 30%	WBC count ($\times 10^9/L$) Initial, 890 Post- WBEx, 434 Hb (g/dL) Pre-WBEx, 4.8 Post-WBEx, 7.5 PLT count ($\times 10^9/L$) Pre-WBEx, 10 Post-WBEx, 127	PLT and RBC transfusion before line placement; no immediate complications; no electrolyte abnormalities or coagulopathy.
3	4.65/female	O+	B-ALL	86 mL/kg × 1; 90 mL/kg × 1	ND	CVL Art line	O– RBCs AB plasma Hct 40%	WBC count ($\times 10^9/L$) Initial, 1119; 80 Post-WBEx, 270.38 Hb (g/dL) Pre- WBEx, 5.4 Post-WBEx, 13.8 PLT count ($\times 10^9/L$) Pre-WBEx, 20 Post- WBEx, 64	Several RBC and PLT transfusions before line and in between separate exchanges; no immediate complications.
2.5	4.70/male	O+	B-ALL	100 mL/kg × 2	40mL/kg/hr	PIV Art line	O– RBCs AB plasma Hct 25%	WBC count ($\times 10^9/L$) Initial, 260.710 Post-WBEx, 52.76 Hb (g/dL) Pre- WBEx, 6.6 Post-WBEx, 6.3 PLT count ($\times 10^9/L$) Pre-WBEx, 41 Post-WBEx, 34	Coagulopathy, tumor lysis syndrome, septic shock; no immediate complications.

B-ALL = B-lineage acute lymphoblastic leukemia; Dx = diagnosis; ND = no data obtainable; WBEx = whole blood exchange transfusion.

TABLE 2
Published cases of leukocytoreduction in acute infant leukemia with hyperleukocytosis and leukostasis

Reference	Pts	Age/weight (kg)	Dx	Mode	Volume/infusion rate [†]	Vascular access	Blood product	Details of procedure	Outcomes
Nguyen et al., 2016 ⁵	1	6 months/ND	B-ALL	AL	ND	ND	ND	No procedure details; anti-coagulation protocol not available.	Catheter-associated thrombus. Patient survived (ND).
Grèze et al., 2014 ⁷	1	2 months/5.0	CMML	AL	1 mL/kg/min over 95 min	DL CVL, SL CVL (cont)	ND	COBE Spectra; no collection details. AC with citrate. No immediate complication.	Death (1)—multiorgan failure 1 week postprocedure.
Woloskie et al., 2001 ¹⁹	1	3 weeks/4.5	ALL	AL	SV × 1/apheresis over 2 hr	CVL (cont)	RBCs/Alb	COBE Spectra; AC with ACD-A; intubated and paralyzed; hemodialysis prophylactically. No immediate complication.	Patient survived (1)—1 week.
Huestis et al., 1992 ¹⁶	1	7 months/7.8	MPAL	AL	DV; 1.3 mL/kg/min	DL CVL (cont)	RBCs/Alb	COBE Spectra; AC with ACD-A. Severely anemic and thrombocytopenic postprocedure.	Death (1)—CMV infection (30 months).
Hayasaka et al., 2015 ¹⁵	5	Newborn/1.7–3.2	DS-TMD	WBEx	DV; over 2 hr	PIV, Arterial (cont)	RBCs, plasma	No procedure details. No immediate complication.	Respiratory failure (4), CCHD (5), bleeding (2), death (2)—cardiopulmonary arrest (1), gastroenteritis (1).
Sykes et al., 2011 ⁹	1	5 months/5.5	ALL	WBEx	SV/ND	CVL (ND)	RBCs	No procedure details. Preprocedure respiratory failure, sinus arrhythmia, and tachycardia; resolved postprocedure.	Patient survived (ND).
Haase et al., 2009 ⁸	3	2–4 months/5.4–6.0	ALL	WBEx	SV × 3 (1), DV(1), TV (1)/1.8–9.3 mL/kg aliquots	CVL or arterial (discont)	RBCs, plasma	Preprocedure, experienced respiratory insufficiency (2), hypovolemic shock (1), coagulopathy (2).	Death (1)—relapse (1). Patient survived (2)—2–10 years.
Strauss et al., 1985 ¹⁷	1	2 days/3.2	AML	WBEx	DV; 6.3 mL/kg aliquots over 1–2 hr	UAC/UVC (cont)	ND	Preprocedure seizures, hypotension, and respiratory failure. No immediate complication.	Death (1)—DIC and ICH; unclear if attributable to the procedure; coagulopathy present.
Warrier et al., 1981 ¹⁸	1	1 days/2.9	AML	WBEx	DV/ND	UVC (discont)	ND	Preprocedure respiratory distress and seizure. No immediate complication.	Death 5 days postprocedure from multiorgan failure.
Runco et al. (this study)	4	2–6 months/4.6–8.9	ALL	WBEx	DV; 2–9 hr	PIV, art line, CVL (cont)	RBCs, plasma	Procedure tolerated without immediate complications.	Death (2)—relapse death (1); BMT-related mortality (1). Survived induction (2)—2–6 months.

AC = anticoagulant; Alb = 5% albumin; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; B-ALL = B-lineage acute lymphoblastic leukemia; BMT = bone marrow transplant; CCHD = complex congenital heart disease; CMML = chronic myelomonocytic leukemia; CMV = cytomegalovirus; cont = continuous exchange; DIC = disseminated intravascular coagulation; discont = discontinuous exchange process; DS = Down syndrome; DV = double volume; Dx = diagnosis; ICH = intracranial hemorrhage; MPAL = mixed phenotype acute leukemia; ND = no data reported; Pts = patients; SV = single volume; TMD = transient myeloproliferative disorder; TV = triple volume; UAC = umbilical arterial catheter; UVC = umbilical venous catheter; WBE = whole blood exchange transfusion.

* Vascular access not specified in terms of lumen numbers. Infusion/withdrawal also classified as continuous or discontinuous or not described.

[†] Total blood volume variable depending on study and calculated between 70 and 100 mL/kg.