How do I perform whole blood exchange?

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There are a number of clinical scenarios in which simultaneous exchange of the patient's plasma and red blood cells (RBCs) are indicated. Some of these clinical indications for therapeutic whole blood exchange (WBEx) include hemolytic disease of the newborn, severe autoimmune hemolytic anemia (AIHA), babesiosis, sickle cell disease, and hyperleukocytosis.[1–4] WBEx has been performed with manual, semiautomated, and fully automated methods using replacements fluids (i.e., RBCs with plasma, RBCs with 5% albumin, and whole blood [WB]) reconstituted to a prespecified target hematocrit (Hct); however, methodologies vary widely and each carry advantages and disadvantages. Here, we describe our combined experiences in performing WBEx, including clinical indications, technical methods, and issues related to their application in the treatment of patients.

MANUAL WBEX

Immune hemolytic anemia

Manual WBEx has been used in pediatric and adult patients with severe AIHA with brisk hemolysis that is unresponsive to standard treatment and simple transfusion.[5–8] Manual WBEx for severe AIHA has several potential advantages over therapeutic plasma exchange (TPE) alone. First and foremost, WBEx can remove both free and RBC-bound antibodies. Furthermore, the infusion and subsequent removal of donor RBCs over the course of several hours permits an "in vivo alloadsorption" of autoantibodies, with reduction in autoantibody titers. In many cases, a single WBEx effected a dramatic decrease in hemolysis.[5–7] WBEx may slow hemolysis through removal of antibodies, sensitized RBCs, and hemoglobin by-products (free iron, methemoglobin)—the latter are hypothesized to synergize and amplify hemolysis in malaria and other chronic non–immune-mediated hemolytic conditions such as sickle cell anemia.[9,10]

At the University of Michigan, manual WBEx method for severe AIHA is performed similar to that for hemolytic disease of the newborn. Reconstituted WB is prepared with type-specific RBCs and plasma to a target Hct of 50% for a 1× to 2× blood volume exchange. We opted for a target Hct of 50% for the replacement fluid given the severity of the hemolytic anemia. Selected RBC units were less than 15 days of age, matched for Rh, Kell, Jk, and other antigens as appropriate based on history and serology, and crossmatched against plasma or adsorbed plasma, if available. Because preparation of reconstituted WB is considered an open system with a 24-hour outdate, we prepared only one reconstituted WB unit at a time (i.e., after dispensing one unit, the next unit was prepared). WBEx was performed by physically removing WB with a syringe, followed by infusion of reconstituted WB. In adult patients, this involved removal of 200 mL (50 mL per draw with 60-mL syringes) over 10 minutes through a triple-lumen central venous catheter, followed by infusion of WB over 1 to 1.5 hours. Overall, it required 20 hours to complete a manual WBEx exchange with 12 units of WB as replacement. For pediatric patients, a similar process was followed using a central or femoral venous catheter (5 mL/kg per draw). We advise against the use of peripherally inserted central catheter lines for manual WBEx based on our experience of losing peripherally inserted central catheter line access early in the process of a manual WBEx in both adult and pediatric patients.

We have performed manual WBEx in three patients with life-threatening AIHA with marked, sustained improvement in two patients. Our first patient was a 19-year-old male with warm AIHA with hemolysis-induced hyperlipidemia, methemoglobinemia, hypertension, volume overload, hypoxia, in vivo RBC agglutination, and worsening hemolysis despite high-dose steroids, intravenous immunoglobulin (IVIG), and splenectomy.[5] After a single WBEx, his hemoglobin was

ABBREVIATIONS: AIHA = autoimmune hemolytic anemia; FCR = fractional of cells remaining; IgM = immunoglobulin M; IVIG = intravenous immunoglobulin; PV = plasma volume; TBV = total blood volume; TPE = therapeutic plasma exchange; WB = whole blood; WBEx = whole blood exchange.

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7.7 g/dL, with resolution of autoagglutination, decrease in autoantibody (titers fell from 1000 to 256), decreased methemoglobin (14% to 1%), and marked improvement in hemolysis and organ function (Fig. 1). Our second case was a 4-year-old with severe warm AIHA due to weak affinity immunoglobulin G. A single WBEx increased his Hct from 5.4% to 33%, decreased methemoglobin (15.4% to 2%), and improved oxygenation (from 83% O_2 on 100% FiO_2 to 99% O_2 on room air). Similar results were reported in a 2-month-old and a 10-year-old who were also treated for AIHA using manual WBEx.[6,7] A single WBEx was also reported to rapidly improve hemolysis due to passenger lymphocyte syndrome in an ABO-incompatible, allogeneic peripheral blood stem cell transplant.[11]

In contrast, WBEx may have limited efficacy in AIHA with a warm immunoglobulin M (IgM) component. We performed three manual WBExs in a posttransplant patient with a severe refractory mixed AIHA that included a warm IgM component. Although there was a transient improvement in Hct, severe hemolysis recurred within 48 to 72 hours after the procedure. Repeated WBEx also failed to suppress hemolysis in two other pediatric patients with warm IgM AIHA.[12,13] WBEx was also ineffective in cold AIHA due to anti-Pr.[14]

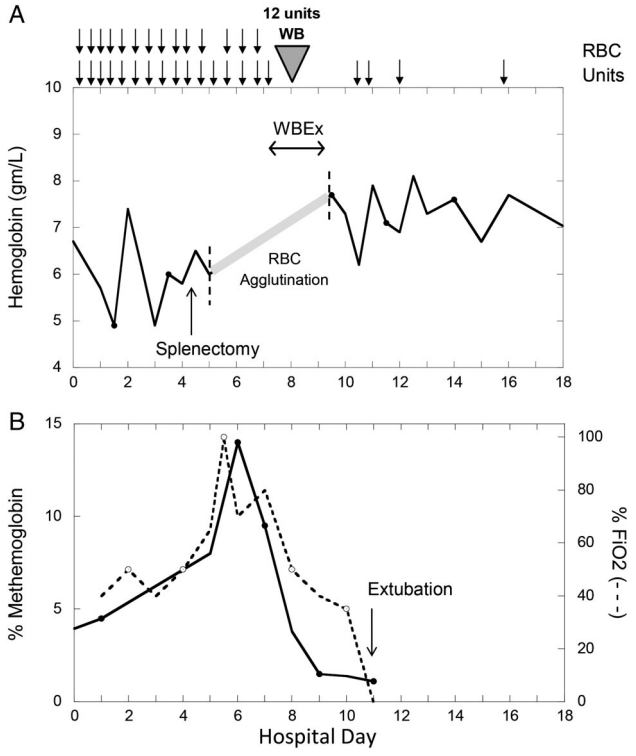

Fig. 1. Clinical course of an adult male with life-threatening AIHA that was treated with manual WBEx. (A) Improved hemoglobin, resolution of RBC autoagglutination and marked decrease in hemolysis and transfusion requirement following WBEx. (B) Decrease in FiO_2 requirement with extubation following manual WBEx and removal of methemoglobin.

Hyperleukocytosis and other indications

Manual WBEx has been used to treat pediatric patients with hyperleukocytosis due to acute leukemia, pertussis, methemoglobinemia, poisoning, neonatal sepsis, thrombotic thrombocytopenia purpura, and Guillian-Barre syndrome.[4,15–25] Manual WBEx may be particularly advantageous in the setting of acute leukemia and sepsis because of the ability to also address anemia and clotting abnormalities. In neonatal sepsis, manual WBEx has been shown to decrease overall mortality and improved renal output.[26] Manual WBEx for thrombocytopenia purpura and other disorders was performed due to the patient's young age or lack of apheresis services.[19–22]

In small children (<10-15-kg body weight), manual WBEx may be a more suitable, safer, and faster option than apheresis. Unlike apheresis, several venous access options are available for manual WBEx. In small children (≤10 kg), leukoreduction can be performed faster by manual WBEx than leukapheresis with equivalent results.[4,16,17] A 10-year review at the University of Michigan showed that leukapheresis in this population took 8 to 24 hours due to access and procedure issues. In children <10 kg, a 2× blood volume leukapheresis averaged 3 hours due to the need for blood prime, slow inlet rate (1-2 mL/kg/min), and delays in establishing an interface. Since 2010, manual WBEx is performed in children <10 kg for hyperleukocytosis.

In hyperleukocytosis and other conditions, manual WBEx has been performed with actual WB, or reconstituted WB with an Hct of 24% to 30%. The exception is WBEx for pertussis, in which an Hct of 40% is recommended.[27] Alternatively, type-specific fresh WB from a donor can be used.[4,19,20]

SEMIAUTOMATED WBEX TRANSFUSION

In the 1940s, WBEx transfusion was first used as a treatment for erythroblastosis fetalis. A continuous process with use of both arterial and venous umbilical vessels for flow was reported by Ata and Holman.[28] In this method, gravity was used to remove blood and replace at equal speeds. The use of dual infusion pumps for an isovolumetric exchange was reported by Cropp.[29] Subsequent modifications of this process introduced dual-lumen catheters and different styles of infusion pumps.[30–32] In these semiautomated WBEx procedures, 1× blood volume exchange is usually performed in an isovolumetric fashion (Fig. 2). The flow rate of the pumps removing and transfusing blood are equivalent, and the replacement fluid is reconstituted WB from the blood bank. Because both circuits can be primed, there is minimal extracorporeal volume. The automation allows for greater flow speeds and more rapid completion of the procedure.

At Roswell Park, we used a semiautomated WBEx method to treat a 53-year-old adult with a malignancy-related AIHA

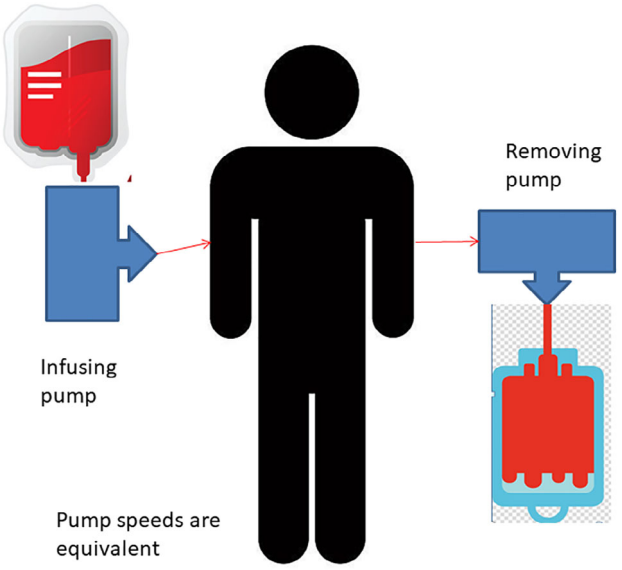

Fig. 2. Semiautomated WBEx procedures are isovolumetric, that is, the flow rates of the pumps removing and transfusing blood are equivalent. [Color figure can be viewed at wileyonlinelibrary.com]

refractory to steroids, IVIG, and the first dose of rituximab.[33] His initial hemoglobin of less than 4 g/dL with accompanying chest pain was considered too low to allow for use of an automated apheresis device. Eight semiautomated WBEx procedures were performed over a 9-day period with approximately 1000 mL of reconstituted WB per procedure. A central line was used for vascular access with the draw and return lines connected to separate infusion pumps. The replacement fluid was RBC reconstituted with 5% human serum albumin to a target Hct within 3% that of the WB being removed to reduce the risk of developing pulmonary edema during the procedure.[34] Limiting the Hct in the replacement fluid was based on a warning to individuals performing automated RBC exchange not to increase the Hct by more than 3% because of the significant risk of inducing pulmonary edema. Changes in the software now prevent this from occurring in the automated system. This patient continued to have active hemolysis but required less intensive RBC transfusion support.

FULLY AUTOMATED, CONTINUOUS-FLOW WBEX TRANSFUSION

Three fully automated, continuous-flow methods for WBEx transfusion have been previously reported (Table 1). Berkessy[35] reported a method using the Kiil dialyzer (both arterial tubing and venous tubing are pumped by the same roller-pump element to maintain constant blood volume) to treat hepatic coma and poisoning with nondialyzable substances. Dorman[2] successfully treated an adult patient with fulminant babesiosis with WBEx transfusion using the COBE Spectra RBC Exchange protocol (Terumo BCT) and the following exchange program parameters: pre-exchange Hct, 32%; replacement fluid Hct, 33% (RBC reconstituted with plasma); target Hct, 30%; and fractional of cells remaining (FCR), 30% (fluid balance percentage was not reported). Li et al.[36] reported clinical outcomes from a cohort of 30 adult patients with severe AIHA treated with WBEx transfusion with the COBE Spectra TPE protocol. This procedure, however, required running the TPE procedure in manual mode so that the RBC line valve is closed to divert separated RBCs and plasma together into the discard bag via the plasma line. Replacement fluids (donor RBCs and plasma) were not reconstituted beforehand but mixed in real-time within the replacement

TABLE 1. Fully automated, continuous-flow methods for WBEx transfusion

Author (Year)	Instrument	Advantages	Disadvantages	Technical aspects
Berkessy (1972)	Kiil dialyzer	Fully automated, continuous flow	Historical technology	Both arterial tubing and venous tubing are pumped by the same roller-pump element to maintain constant blood volume.
Dorman (2000)	COBE Spectra, RBC exchange protocol	Fully automated, continuous flow	Recently phased-out technology; reconstituting RBCs to the intended Hct is labor intensive	Reconstitute RBCs with plasma to a target Hct as close to the patient's pre-exchange Hct, and program FCR at 30%.
Li (2015)	COBE Spectra, TPE protocol	Fully automated (in manual mode), continuous flow	Recently phased-out technology; reconstituting RBCs in real-time may result in variable replacement fluid Hct	RBC line valve is closed so that WB is diverted (via the plasma line) into the discard bag. Replacement fluid Spike 1 to donor RBC, and spike 2 to donor plasma.
Lin (2019)	Spectra Optia, RBC exchange protocol	Fully automated, continuous flow	Reconstituting RBC to the intended Hct is labor intensive	Reconstitute RBC with compatible fluid to Hct as close to the patient's pre-exchange Hct, and program FCR at 30%-35%.

[7] FCR, fractional cell remaining.

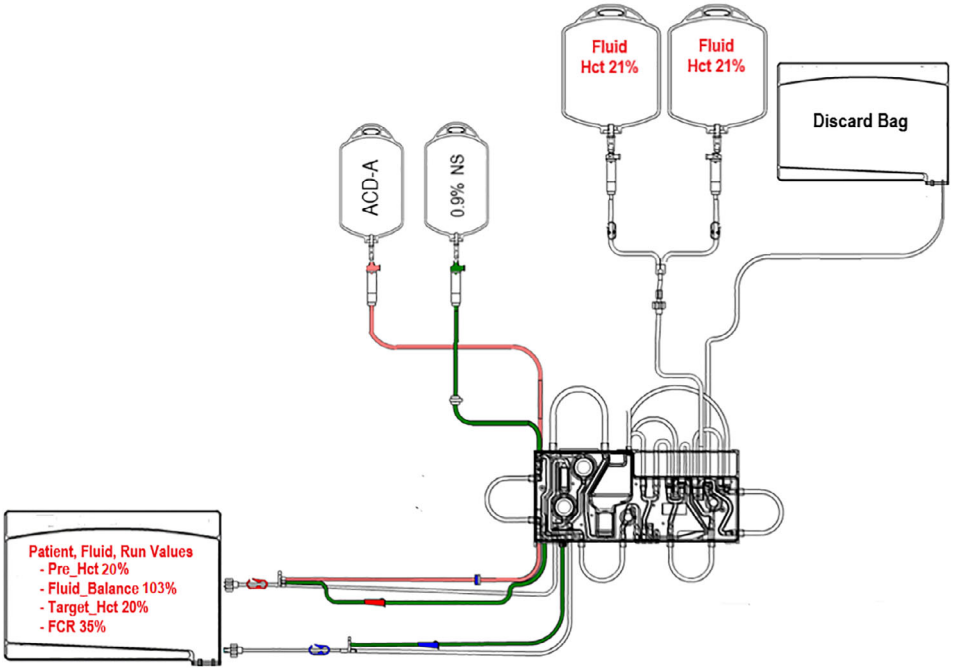

Fig. 3. Fully automated, continuous-flow method for WBEx with the Spectra Optia. [Color figure can be viewed at wileyonlinelibrary.com]

fluid tubing (i.e., replacement fluid Spike 1 to donor RBC, and Spike 2 to donor plasma).

In comparison, Bloodworks' validated WBEx protocol using the Spectra Optia is fully automated and takes advantage of US Food and Drug Administration 510(k) cleared RBC exchange protocol.[37] Based on the observation at Bloodworks that a median plasma volume (PV) of 0.34 (interquartile range, 0.33-0.36 PV) is simultaneously exchanged in patients with sickle cell anemia on a chronic RBC exchange program with use of replacement fluid with median Hct of 56%, and applying the principle of RBC conservation (i.e., [Total Blood Volume (TBV) × target Hct] + [Remove Volume × Remove Hct] = [TBV × pre-Hct] + [Replacement Volume × Replacement Fluid Hct]) in a closed patientapheresis system, approximately a 1.0 PV can be exchanged while simultaneously achieving an FCR target of 35% by simply diluting the replacement fluid to the patient's pre-exchange Hct.[38]

This fully automated WBEx procedure was used to treat a 50-year-old adult with a new severe symptomatic warm AIHA and an initial hemoglobin of 4.4 g/dL refractory to steroid, IVIG, and rituximab despite a total of 40 units of Rh and Kell antigen-matched RBC transfusion support over 2 weeks.[39] A total of approximately 6.7 L of replacement fluid (RBC reconstituted with 5% albumin to an expected Hct of 21%) was used to achieve target Hct of 20% and FCR of 35% (Fig. 3). The patient tolerated the WBEx procedure well, the initial run values were attained, and the anti-human globulin autoantibody titer fell from 8 to 2. The patient eventually recovered after a prolonged hospital stay that included additional immunosuppressive therapies, including cyclophosphamide, and splenic-artery embolization.

CONCLUSION

As described, experiences from multiple institutions demonstrated that it is feasible to perform WBEx for several clinical indications. While the reported case number is small, some clinical benefit of WBEx has been shown for certain clinical indications. All of the reported methods and techniques have their own unique setup and challenges. More studies and technology advancement are needed in the future to firmly establish clinical indications as well as simplify WBEx technology.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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