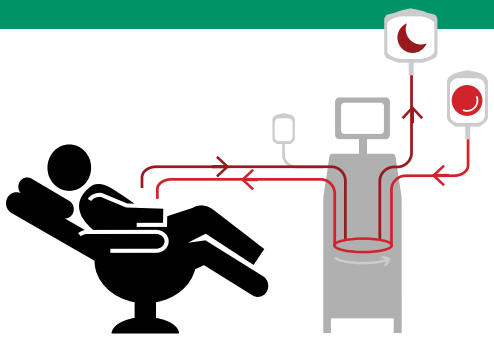
TERUMO BLOOD AND CELL TECHNOLOGIES

Manage the Balancing Act of Sickle Cell Disease With Automated Red Blood Cell Exchange (RBCX)

Automated RBCX as an Established Transfusion Therapy



Automated RBCX is an established transfusion therapy for sickle cell disease patients that, unlike simple transfusion and manual exchange, efficiently and rapidly removes sickled cells and replaces them with healthy donor cells using an apheresis device.

During a simple (top-up) transfusion, a patient receives healthy donor red blood cells, but none of the patient's blood is removed. In a manual exchange procedure, a clinician removes whole blood and subsequently replaces it with red blood cells.

Evidence-Based Guidance for Automated RBCX in Sickle Cell Disease

American Society for Apheresis (ASFA) 2019[1]	■ Acute stroke – Category I, Grade 1C ■ Acute chest syndrome (ACS), severe – Category II, Grade 1C ■ Stroke prophylaxis – Category I, Grade 1A ■ Pregnancy – Category II, Grade 2B ■ Recurrent vaso-occlusive pain crisis (VOC) – Category II, Grade 2B ■ Pre-operative management – Category III, Grade 2A
American Society of Hematology (ASH) 2020[2,3]	■ Chronic transfusions – conditional recommendations, very low certainty evidence ■ Severe ACS – conditional recommendations, very low certainty evidence ■ Moderate ACS – conditional recommendations, very low certainty evidence ■ Acute neurological deficits including transient ischemic attack (TIA) – conditional recommendations, very low certainty evidence
National Heart, Lung and Blood Institute (NHLBI) 2014[4]	■ Symptomatic severe ACS – strong recommendation, low quality of evidence ■ Stroke – moderate recommendation, low quality of evidence ■ Child with transcranial Doppler (TCD) reading > 200 cm/sec – strong recommendation, high quality of evidence (chronic exchange or simple transfusion) ■ Adults and children with previous clinically overt stroke – moderate recommendation, low quality of evidence (chronic exchange or simple transfusion)

More Time for Life, Less Time in the Hospital

The average procedure time for automated RBCX is typically shorter than the average manual exchange or simple transfusion procedure time. The average automated RBCX procedure time ranges **from 86 to 120 minutes**, compared to 120 to 245 for manual exchange.[5,6,7,8,9,10,11]

Procedures can also be carried out less frequently than simple transfusion and manual exchange. The average number of days between procedures for automated RBCX ranges from 28 to 47.[5,6,8,12]

The average automatic RBCX procedure time is about half of the time of a manual exchange procedure. [5,6,7,8,9,10]

Vaso-Occlusive Crisis (VOC)

Vaso-occlusive crisis is the most common complication of sickle cell disease and **accounts for more than 90% of acute hospital admissions**; it typically occurs in the extremities, back, joints, abdomen or chest.[13]

Automated RBCX is the better option for most patients at risk of vaso-occlusive events because unlike simple transfusion, the procedure does not increase blood viscosity.[2,14]

In a retrospective study 27 patients with recurrent painful crises were placed on a chronic automated RBCX program. Of the 27 patients, 70% showed a sustained reduction in the number of emergency hospital visits.[15]

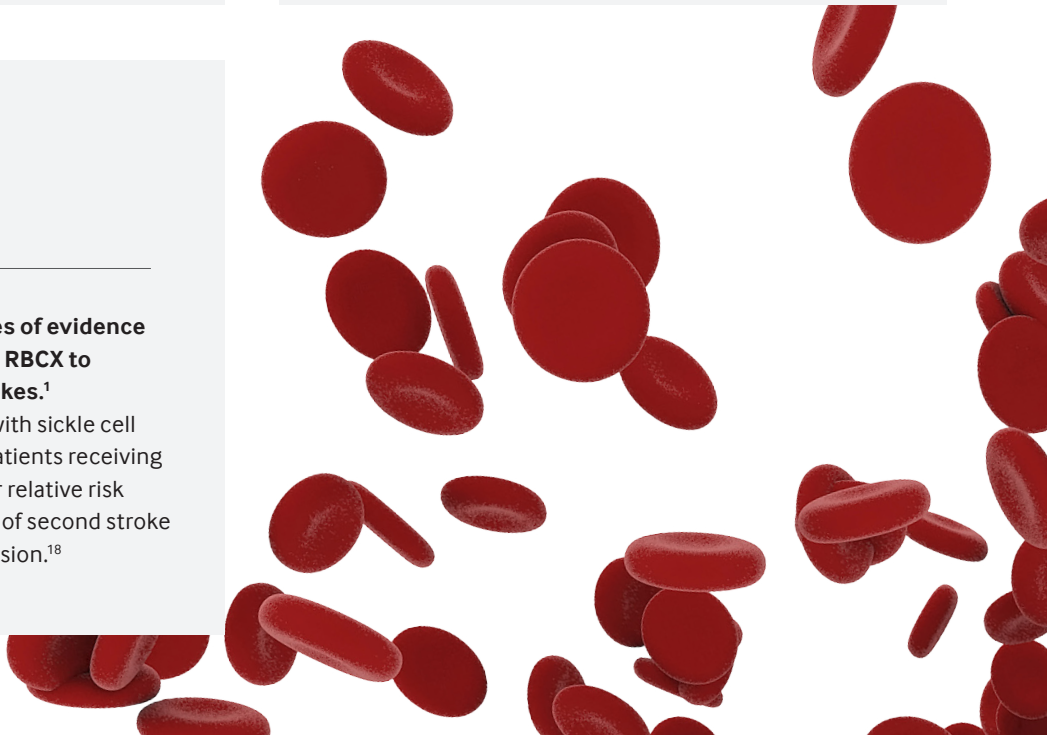
Acute Chest Syndrome (ACS)

ACS is the second most common cause for hospitalization in patients with sickle cell disease. Because recurrent episodes of ACS in childhood may lead to sequelae, it is imperative to reduce the frequency of future episodes by implementing preventive interventions.[16]

In 44 sickle cell disease patients who had an ACS episode, clinical respiratory score improved from 4 to 2 within 24 hours of automated RBCX, performed on average on the second day of admission (of 7 total median hospitalization days).[17]

Stroke Prevention

ASFA has summarized several bodies of evidence that show the efficacy of automated RBCX to prevent primary and secondary strokes.[1]
A retrospective study of 137 children with sickle cell disease and previous stroke showed patients receiving simple transfusion had a 5-fold greater relative risk (95% confidence interval = 1.3 to 18.6) of second stroke than those receiving exchange transfusion.[18]



Find the Balance: How Automated RBCX Helps Manage Sickle Cell Disease

Pregnancy

More than 50% of obstetric patients with sickle cell disease will have a pain crisis during pregnancy, and these can be challenging to manage.[19]

In a single-center, retrospective, and cross-sectional study of 37 pregnant women diagnosed with sickle cell disease, 24 patients received prophylactic automated RBCX and 13 patients did not. Prophylactic automated RBCX significantly reduced maternal mortality and the incidence of VOC compared to those patients who did not receive automated RBCX.[19]

Iron Overload

Automated RBCX can prevent and reduce iron overload with minimal or no iron chelation compared to simple transfusion or manual exchange.[5,9,11,20,21]

In a prospective study including retrospective data, 57 patients with sickle cell disease switched to an automated RBCX program after a median of 3.7 years of receiving chronic simple transfusion. After a median of 4.2 years of receiving RBCX, **median ferritin levels decreased by 84%** from a median of 2,471 ng/mL to a median of 392 ng/mL.[22]

Alloimmunization

While automated RBCX exposes patients to 20% to 50% more red blood cell units (RBCUs) than conventional transfusion therapy, in theory increasing the risk of alloimmunization, it has been shown in several studies that **automated RBCX was associated with a lower rate of alloimmunization** than simple transfusion.[20,23,24]

A retrospective study of 188 patients with sickle cell disease receiving transfusion therapy showed that **automated RBCX was associated with a lower rate of alloimmunization compared to simple transfusion over 5 years.**[20]

	RBCX (n = 49)	Simple Transfusion (n = 139)	Statistical Significance
Alloimmunization/RBCU ratio (per 1000)	**1.6**	11.6	*P* < 0.0001
RBCUs/patient	**206**	19	*P* < 0.0001
Proportion of patients with alloantibodies, n (%)	**16 (33%)**	31 (22%)	*P* = 0.1797

Automated RBCX was associated with a lower rate of alloimmunization compared to simple transfusion over 5 years.[20]

Maternal mortality and the incidence of VOCs were significantly lower in pregnant sickle cell disease patients who received prophylactic automated RBCX.[19]

After a median of 4.2 years being on a chronic automated RBCX program, patient ferritin levels decreased by a median of 84%.[22]

Apheresis-Related Safety Information

- Contraindications for the use of apheresis system are limited to those associated with the infusion of solutions and replacement fluids as required by the apheresis procedure and those associated with all types of automated apheresis systems.
- **Adverse events of apheresis procedures can include:** Anxiety, headache, light-headedness, digital and/or facial paresthesia, fever, chills, hematoma, hyperventilation, nausea and vomiting, syncope (fainting), urticaria, hypotension, allergic reactions, infection, hemolysis, thrombosis in patient and device, hypocalcemia, hypokalemia, thrombocytopenia, hypoalbuminemia, anemia, coagulopathy, fatigue, hypomagnesemia, hypogammaglobulinemia, adverse tissue reaction, device failure/disposable set failure, air embolism, blood loss/anemia, electrical shock, fluid imbalance and inadequate separation of blood components.[25]
- **Reactions to blood products transfused during procedures can include:** Hemolytic transfusion reaction, immune-mediated platelet destruction, fever, allergic reactions, anaphylaxis, transfusion-related acute lung injury (TRALI), alloimmunization, posttransfusion purpura (PTP), transfusion-associated graft-versus-host disease (TA-GVHD), circulatory overload, hypothermia, metabolic complications and transmission of infectious diseases and bacteria.[26,27]
- **Restricted to prescription use only.**

Operators must be familiar with the system's operating instructions. Procedures must be performed by qualified medical personnel.

References

[1] Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice — evidence-based approach from the writing committee of the American Society for Apheresis: the eighth special issue. *J Clin Apher.* 2019;34(3):171-354.

[2] Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. *Blood Adv.* 2020;4(2):327-355.

[3] DeBaun MR, Jordan L, King A, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv.* 2020;4(8):1554-1588.

[4] National Heart, Lung, and Blood Institute. Evidence-Based Management of Sickle Cell Disease Expert Panel Report. 2014.

[5] National Institute for Health and Care Excellence. Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease. https://www.nice.org.uk/guidance/mtg28. Medical technologies guidance (MTG28). Published March 2016.

[6] Kuo K, Ward R, Kaya B, Howard J, Telfer P. A comparison of chronic manual and automated red blood cell exchange transfusion in sickle cell disease patients. *Br J Haematol.* 2015;170(3):425-428.

[7] Howard J. The role of blood transfusion in sickle cell disease. *ISBT Science Series.* 2013;8:225-228.

[8] Al-Salem AH. Medical and Surgical Complications of Sickle Cell Anemia. Springer; 2016.

[9] Singer T, Quirolo K, Nishi K, Hackney-Stephens E, Evans C, Vichinsky E. Erythrocytapheresis for chronically transfused children with sickle cell disease: an effective method for maintaining a low HbS level and reducing iron overload. *J Clin Apher.* 1999;14(3):122-125.

[10] Duclos C, Merlin E, Paillard C, et al. Long-term red blood cell exchange in children with sickle cell disease: manual or automatic? *Transfus Apher Sci.* 2013;48(2):219-222.

[11] Dedeken L, Le PQ, Rozen L, et al. Automated RBC exchange compared to manual exchange transfusion for children with sickle cell disease is cost-effective and reduces iron overload. *Transfusion.* 2018;58(6):1356-1362.

[12] Singer T, Quirolo K, Nishi K, Hackney-Stephens E, Evans C, Vichinsky E. Erythrocytapheresis for chronically transfused children with sickle cell disease is cost-effective and reduces iron overload. *Transfusion.* 2018;58(6):425-428.

[13] Sins JWR, Mager DJ, Davis SCAT, Biemond BJ, Fijnvandraat K. Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: a systematic review. *Blood Adv.* 2017;1(19):1598-1616.

[14] Houwing ME, de Pagter PJ, van Beers EJ, et al. Sickle cell disease: clinical presentation and management of a global health challenge. *Blood Rev.* 2019;37:100580.

[15] Tsitsikas DA, Sirigireddy B, Nzouakou R, et al. Safety, tolerability, and outcomes of regular automated red cell exchange transfusion in the management of sickle cell disease. *J Clin Apher.* 2016;31(6):545-550.

[16] Jain S, Bakshi N, Krishnamurti L. Acute chest syndrome in children with sickle cell disease. *Pediatr Allergy Immunol Pulmonol.* 2017;30(4):191-201.

[17] Velasquez MP, Mariscalco MM, Goldstein SL, Airewele GE. Erythrocytapheresis in children with sickle cell disease and acute chest syndrome. *Pediatr Blood Cancer.* 2009;53(6):1060-1063.

[18] Hulbert M, Scothorn D, Panepinto J, et al. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. *J Pediatr.* 2006;149(5):710-712.

[19] Asma S, Kozanoglu I, Tarım E, et al. Prophylactic red blood cell exchange may be beneficial in the management of sickle cell disease in pregnancy. *Transfusion.* 2015;55(1):36-44.

[20] Michot J, Driss F, Guitton C, et al. Immunohematologic tolerance of chronic transfusion exchanges with erythrocytapheresis in sickle cell disease. *Transfusion.* 2014;55(2):357-363.

[21] Kalff A, Dowsing C, Grigg A. The impact of a regular erythrocytapheresis programme on the acute and chronic complications of sickle cell disease in adults. *Br J Haematol.* 2010;149(5):768-774.

[22] Stanley HM, Friedman DF, Webb J, Kwiatkowski JL. Transfusional iron overload in a cohort of children with sickle cell disease: impact of magnetic resonance imaging, transfusion method, and chelation. *Pediatr Blood Cancer.* 2016;63(8):1414-1418.

[23] Wahl SK, Garcia A, Gildengorin G, Quirolo K, Vichinsky E. Lower alloimmunization rates in pediatric sickle cell patients on chronic erythrocytapheresis compared to chronic simple transfusions. *Transfusion.* 2012;52(12):2671-2676.

[24] Lombardo T, Rosso R, La Ferla A, et al. Acute chest syndrome: the role of erythro-exchange in patients with sickle cell disease in Sicily. *Transfus Sci.* 2003;29(1):39-44.

[25] Daver N, Kantarjian H, Marcucci G, et al. Clinical characteristics and outcomes in patients with acute promyelotic leukaemia and hyperleucocytosis. *Br J Haematol.* 2015;168(5):646-653.

[26] AABB. Circular of Information for the Use of Human Blood and Blood Components. Bethesda, MD: AABB; 2017.

[27] European Directorate for the Quality of Medicines & HealthCare (EDQM). Guide to the Preparation, Use and Quality Assurance of Blood Components. 20th edition. Strasbourg, France: EDQM Council of Europe; 2020.

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