2015 - 04
Volume 9, Issue 1

Bloody Good News

Newfoundland and Labrador Provincial Blood Coordinating Program

Special Interest Articles:

- **Long Acting Factor Concentrates**
- **FEIBA**

Individual Highlights:

Cytomegalovirus – CMV Sero-Negative or CMV Safe

Cytomegalovirus (CMV) is a common white blood cell herpes virus that affects people of all ages. Primary CMV infection in immunocompetent patients is normally mild with symptoms ranging from none to mononucleosis-type syndrome. These symptoms include fever, malaise and lymphadenopathy. It does not usually cause any long-term health problems. CMV is of no risk for the majority of transfusion recipients, as the virus is inactive in most donors. CMV is only transmissible when active. Therefore, it is unlikely to be transmitted through a blood transfusion. Thus, CMV sero-negative or CMV safe blood products are not required, or requested, for most transfusions.

However, certain patient populations can benefit from CMV safe or CMV sero-negative blood components. CMV infection can be overwhelming or even fatal in patients with weakened immune systems. This patient population includes fetuses (intrauterine transfusion), low birth weight premature infants, neonates under 28 days old, and CMV seronegative pregnant women.

CMV sero-negative blood components have tested negative for CMV antibodies whereas CMV safe blood components are CMV seronegative or leukoreduced. There has been much controversy about which product is preferred for transfusion to the at risk patient populations.

Canada's blood supply has been leukoreduced since 1999. Leukocyte reduction is defined by AABB as less than 5×10^6 residual donor white blood cells (WBC) per final product. Many studies have demonstrated that in the era of universal leukoreduction, there is little or no need for CMV testing of donors and CMV safe products are acceptable alternatives.

The National Advisory Committee (NAC) on Blood and Blood Products issued the following statement: "CMV safe and CMV IgG seronegative products be considered equivalent for the majority of patient populations including adult and pediatric Hematopoietic stem cell recipients, CMV seronegative patients who may require future transplant and immune-deficient patients. Due to significant controversy and lack of evidence on the need for the provision of CMV seronegative products in addition to leukodepletion in the following (3) three patient groups -intrauterine transfusion, neonates under 28 days of age, and elective transfusion of CMV seronegative pregnant women, NAC recommends following local guidelines for providing CMV negative versus CMV safe products (NAC 2014).
The NAC is currently reviewing this statement in light of a recent study by the Australian Red Cross. *(Vox Sanguinis (2015).*

In circumstances where CMV negative blood components are indicated, but not available, a physician may choose a CMV safe product as an alternative.

The prevalence of past exposure to CMV, as indicated by a positive IgG, varies markedly throughout the world ranging from 100% in adults in developing countries versus approximately 40% at age 20 and 80% at age 60 in developed countries. This shows the majority of donors have had exposure to CMV.

CMV safe may be a practical transfusion option.

Janet Vaughan, a physician and experimental physiologist who studied blood diseases, blood transfusion, the treatment of starvation, and the effects of radioactivity on bone and bone marrow, was the daughter of a well-known educator, William Wyamar Vaughan, headmaster of the Rugby School. One of her aunts was a founder of Somerville College, Oxford.

She was educated at home until she was fifteen. She then went to North Foreland Lodge and from there to Somerville College, entering after passing the entrance examinations on her third try.

She began work on bone marrow diseases and produced the textbook, THE ANAEMIAS in 1934.

The Medical Research Council adopted her suggestion that blood be banked in the event of a war. She became director of the North West London Blood Supply at the beginning of World War II. Before the war ended, she was awarded an Order of the British Empire for her work.
Vaughan held a significant role supporting women in Medicine. She was made a Fellow of the Royal Society in 1979.
She died in 1993.

Long Acting Factor Concentrates

Patients with Hemophilia A or Hemophilia B require lifelong treatment to replace the blood clotting factors by infusing factor concentrates. These concentrates can be derived from human plasma or genetically engineered with DNA technology (recombinant).

When severe, hemophilia causes life-threatening bleeding episodes. People who suffer from severe Hemophilia must follow a prophylactic regimen to prevent bleeding. Less severe cases may require factor replacement only to control a bleeding episode or before invasive procedures.

Extending the half-life of new products used to treat Hemophilia A and Hemophilia B has been one of the main areas of research for pharmaceutical companies. The term half-life is used to describe how long it takes for one half of a dose of drug to be cleared from the blood. Factors with a longer half-life have obvious benefits for the patient, as fewer infusions mean a better quality of life and decreased risk of adverse reactions as the product is administered less frequently.

In 2014, Health Canada approved a long-acting recombinant Factor IX Fc fusion protein – Alprolix (manufactured by Biogen Idec.) This marks the first significant advance in the treatment of hemophilia B in seventeen years (Benefix®).

Alprolix temporarily replaces missing coagulation Factor IX. It contains the Fc region of human IgG. The half-life of Alprolix is 86.52 hours. This allows infusions to be reduced to once a week or every ten to fourteen days.

Some concerns raised by the bleeding disorder community include:

a) Is there an increased risk of developing inhibitors when patients are switched to or started on these products?

This is not a new concern in factor replacement therapy. Many studies have confirmed that switching patients to a new product does not increase the risk of inhibitors. In some countries, patients are routinely switched between products as new drug purchase agreements are made. There is no difference in the incidence of inhibitors in this group, as compared to groups that have remained on the same product since the start of their therapy.

b) Is the use of pegylation (PEG) which used in the formulation of Alprolix to enhance the drugs half-life, safe?

Since factor replacement is a life-long treatment, some have wondered if PEG will build up to toxic levels in the liver. In response to this, researchers have cited the long safety record of other drugs, which include PEG in their formulation and the fact that the amount of PEG infused with the product is minimal. No toxic effects of PEG have been reported to date.

Alprolix is being reviewed by Canadian health authorities and Canadian Blood Services. Decisions will be available soon as to when this product will be approved for distribution in Canada.

The continued evolution of factor replacement therapy provides the bleeding disorder community a new way to manage their condition.

Educational In-services

Leona and Daphne have begun regional in-service sessions.

Leona and Daphne share a wealth of knowledge related to transfusion from the Laboratory and the Nursing perspectives.

The plan is to resurrect the educational activities of the program and provide site visits to various hospitals within the health care regions, as well as to the College of the North Atlantic and the Schools of Nursing Studies.

If you would like an in-service, please feel free to contact us at the numbers and emails provided on page 4 of the newsletter.

Newfoundland Labrador

FEIBA

FEIBA™ – Factor VIII inhibitor bypassing agent is an activated prothrombin complex concentrate containing activated factor VII, and non-activated factors II, IX and X.

FEIBA™ is indicated for the control of spontaneous bleeding episodes, to cover surgical interventions in hemophilia A and B patients who have developed inhibitors to the normal factor VIII and factor IX concentrates and for routine prophylaxis to prevent or reduce bleeding episodes in adults and children over the age of six (6) with hemophilia A or B with inhibitors.

Currently, this is the only labeled use for FEIBA™.

FEIBA™ is currently being used for a variety of unlabeled indications. Some physicians have ordered this product for the reversal of New Oral Anticoagulants (NOAC's) when patients are bleeding or require immediate surgery or for use during cardiac surgery when the patient experiences life-threatening bleeding.

Due to the high risk of thromboembolic events associated with this product, the benefits and risks of unlabeled use should be carefully considered by the physician before use.

In 2013, Thrombosis Canada made the following statement: "It should be recognized that these prohemostastic agents are not NOAC antidotes. It is possible, however, that prohemostatic agents may lessen NOAC-related bleeding. Studies in patients with intracerebral bleeding suggest that although prohemostatic agents can limit the extent of bleeding, their effect on mortality and disability might be minimal. The use of prohemostatic agents should be considered, although supportive clinical data is lacking."

The American Society of Hematology, after a retrospective review of patients receiving NOACs and requiring urgent reversal of anticoagulation between January 2013 and June 2014, came to the following conclusion: "The use of FEIBA™ for reversal of NOAC effect for urgent surgery in this cohort of patients was effective and not associated with adverse thrombotic complications. Prospective studies evaluating use of potential benefits and harms of FEIBA™ for reversal of NOACs in patients requiring emergent surgery are needed."

Maybe there is a time for FEIBA™ in reversing these new oral anticoagulants.

What about during cardiac surgery?

Baxter, the company which manufactures FEIBA™ has made the following statement: "FEIBA™ is contraindicated in cardiac surgery involving cardiopulmonary bypass and procedures involving extracorporeal membrane oxygenation (ECMO) due to the high risk of thrombotic adverse events."

Despite this, in 2014, the American Association for Thoracic Surgery had the following conclusion concerning the use of FEIBA™ for cardiac surgery: "Our initial experience with FEIBA™ administration for the rescue treatment of postoperative coagulopathy and life-threatening bleeding has been favorable. Further studies are indicated to confirm its efficacy and safety and determine specific clinical indications for its use in patients undergoing cardiac surgery."

There is still much work to be done on the safe appropriate use of blood and blood products.

Case Study #22

A 55 year old oncology patient was ordered one adult dose of platelets. The patient was immune-compromised on chemotherapy. No premedication was administered. Although the patient's temperature was normal pre-transfusion, it had been noted that the patient had a fever earlier in the day as well as the day before. The transfusion was initiated and within five (5) minutes, the patient experienced an increase in blood pressure, shortness of breath, and hypoxia. The oxygen saturation was in the 80's. Ten (10) mLs of platelets were transfused. The transfusion was stopped.

<u>Pre transfusion</u>
B/P: 122/64
Heart rate: 114
Respiratory Rate: 20
Temperature: 36.9

Post transfusion:
BP 118/59
Heart rate: 120
Respiratory rate: 26
Temperature: 38.0

Supplementary oxygen, Ventolin, antihistamines and steroids were administered. Chest x-rays were normal and blood cultures were negative.

1. Classify type of reaction.

2. What was the relationship of the adverse event to the transfusion?

3. What was the severity of the reaction?

4. What was the outcome of the adverse event?

Newfoundland Labrador

Age of Blood Evaluation (ABLE) Study Results – Impacts on Patients

Red blood cells for transfusion can be stored up to 42 days in Canada. Although most blood is transfused within 28 days, there has been a long held belief that fresher blood improves outcomes in critically ill patients.

The results of a five-year multicenter, randomized, blinded trial conducted in 64 centres in Canada and Europe was released in the New England Journal of Medicine in March 2014. The study included 2412 patients, separated into 2 arms whereby 1211 patients received leukoreduced red cells 6.1 ± 4.9 days old, whereas the second arm of 1219 patients received leukoreduced red blood cells that were on average 22.0±8.4 days old. A restrictive transfusion strategy with a hemoglobin threshold of 7.7 g/dL was used for most patients. As SAGM suspended red cells are the standard product supplied in Canada and Europe, the trial used SAGM rather than AS-3 additive solution component.

Fresh blood cells were stored for less than 8 days. Standard issue red cells were defined as the oldest compatible units available.

The primary outcome of 90 day mortality was not decreased in patients who received fresh red blood cells versus those who received standard issue red cell components.

The secondary outcome showed no significant difference in mortality based on other patient information documented throughout the trial. Documentation included organ dysfunction, infections of various types, length of stay in ICU and in the hospital, as well as duration of supports such as respiratory, renal and hemodynamic. Transfusion reactions and adverse events were recorded daily.

The conclusion of the trial noted that the 90-day mortality rate among critically ill adults did not decrease when patients were transfused with fresh red cells as compared to the standard issue red cells.

There was no assessment on whether the use of 35 to 42 day old red blood cells resulted in harm.

(*New England Journal of Medicine, March 17, 2015 at NEJM.org*)

SCIG Home Infusion Program

Immune globulin therapy has been a treatment for patients with immune deficiencies since the early 1950's.

Since that time, the categories of diseases successfully treated with immune globulin therapy has expanded, as has the variety of immune globulin products available to treat these patients.

Initially patients received treatment intravenously in hospitals as in-patients, then progressed to ambulatory treatment clinics and today in a home environment for specific patient groups. The NL PBCP is working with Regional Health Authorities (RHAs) to implement a home infusion program for Subcutaneous Immune Globulin (SCIG). This program will allow certain patients such as those with Primary Immune Deficiency and Secondary Immune Deficiency to infuse immune globulin at home.

These patients will be trained to self-administer SCIG based on the dose and frequency as prescribed by their health care provider. This will provide a greater level of self-management and improve the quality of life for these patients as they will not have to present at hospital for infusions, take time off from school or work, and will enjoy the flexibility provided to administer at times convenient to them.

We anticipate this program will launch in the early summer with a few patients enrolling. Growth will be progressive and feedback from patients will provide direction to grow and improve the program as it moves forward. We are excited to see this project roll out across the RHAs.

Newfoundland and Labrador Provincial Blood Coordinating Program

P.O.Box 8700
St. John's, NL
A1B 4J6

PHONE:
(709) 729-5246
(709) 729-6573
(709) 729-5250

FAX:
(709) 729-4009
E-MAIL:
marilyncollins@gov.nl.ca
leonabrowne@gov.nl.ca
daphneosborne@gov.nl.ca

For reference documents including policies visit:
http://www.health.gov.nl.ca/health/bloodservices/index.html

Newfoundland Labrador

Case Study #22 Interpretation

1. *Type of Reaction –* ***TAD***
2. *Relationship of adverse event to transfusion –* ***Possible***
3. *Severity of the reaction –* ***Grade 2***
4. *Outcome –* ***MINOR OR NO SEQUELAE***

Leadership and learning are indispensable to each other.
John F. Kennedy, *speech prepared for delivery in Dallas the day of his assassination, November 22, 1963, 35th president of US 1961-1963 (1917 - 1963)*