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University of Alberta

An Analysis of Transfusion Practices and Mortality in Neonates at the University of Alberta Neonatal Intensive care Unit: January 1978 to April 1992

by

Anjali Chudasama

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

in

Medical Sciences – Public Health Sciences

Edmonton, Alberta
Fall 1999

University of Alberta

Library Release Form

Name of Author: Anjali Chudasama

Title of Thesis: An Analysis of Transfusion Practices and Mortality in Neonates at the University of Alberta Neonatal Intensive Care Unit: January 1978 to April 1992

Degree: Master of Science

Year this Degree Granted: 1999

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Dedication

The author wishes to dedicate this piece of work to her paternal grandparents C.G. Chudasama and V.C. Chudasama as well as her maternal grandparents the late D.K. Jadeja and M.D. Jadeja. Finally, with heartfelt gratitude, admiration and love, the author dedicates the thesis to her parents Uday and Sushil Chudasama.

Abstract

Neonates are the most frequently transfused of all patient population. This is due primarily to prematurity and the severity of other illnesses. Although blood transfusions are life saving interventions, they carry the risk of transfusion associated infectious diseases such as Hepatitis C (HCV). There were 7993 eligible patients admitted to the University of Alberta Neonatal Intensive Care Unit (NICU) between January, 1978 and April, 1992. Patient information such as birthweight, gestational age, mortality and transfusion was collected and recorded by reviewing patient charts. Birthweight, gestational age and transfusion were risk factors for neonatal mortality. Survival for infants with low birthweights, low gestational age and infants receiving 50 or more units of various blood products was worse. Most of the changes in transfusion practices occurred in 1985 and 1989 upon the introduction of screening tests for HIV and HCV respectively. Transfusions in neonates are complex and require further research.

Acknowledgement

I would like to acknowledge and express sincere gratitude to the following for their contribution to this study.

The members of my supervisory committee, Dr Patrick Hessel, Dr Jutta Preiksaitis, Dr Steve Newman and Dr Leslie Smith, for their support and supervision of this research project. Particulary, Dr Hessel for his guidance, support and generosity, and Dr. Preiksaitis for the wonderful opportunity.

To Roseanne Buijis, Maryze Pantin, Elizabeth Pantin and Dr. Margaret Ritchie for database support and management.

To Rae Roulston and the support staff in the department of Public Health Sciences.

The Canadian Red Cross for their generous funding of this study.

And finally, I would like to thank Premal Amin, John Sharma, and Narmatha Thanigasalam as well as my fellow graduate students for their continual encouragement and support.

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Chapter 1

Introduction

Study Objectives

The objectives of this study were:

- To determine the relationship between mortality within the Neonatal Intensive Care Unit (NICU) from January 1978 to April 1992 (not including 1982-1983) and several risk factors such as birthweight (grams), gestational age (weeks), length of stay (days) and transfusion (unit and donor exposure).
- To describe the trend in unit and donor exposure for transfused neonates and changes in the types of blood products given in the NICU from January 1978 to April 1992 (not including 1982-1983).
- To assess the public health impact of transfusions in neonatal populations by estimating the number of transfused survivors from the NICU that may have been exposed to Hepatitis C from January 1978 to April 1992 (not including 1982-1983).

Purpose

There have been numerous studies conducted in very low birthweight infants and transfusion practices in Neonatal Intensive Care Units (NICU) (Paul et al, 1997; Widness et al, 1996; Ringer et al, 1998). However, a search of the literature to our knowledge produced one reported nationwide study on outcome of very low birthweight (VLBW) neonates treated in the NICU (Malaysian Very Low Birth Weight Study Group, 1997). The present study differs from this previous study in that it provides insight into the mortality of patients in the NICU over all birthweight and gestational age categories and various lengths of stay. Assessing the changes in transfusion practices will help determine if the guidelines for transfusion of various blood products have been followed over the years and the impact that blood product screening procedures have on

transfusion practices. In the past, the incidence and the number of infected individuals with transfusion transmitted infectious diseases has been over-estimated (Vamvakas and Taswell, 1994). Estimation of HCV infection in transfused neonates in this study will provide a more accurate picture by considering the number and proportion of blood products administered to neonates who do not survive. Thus this study provides insight into the differences that exists between these infants, children and adults in terms of survival, mortality and prognosis.

Format of the Thesis

The format of this thesis is paper-based and consists of three papers. Chapters 4 and 5 in combination and Chapter 6 are to be submitted for publication. The introduction, literature review and general conclusions and discussions are added for the purposes of the Masters of Science thesis.

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Chapter 2

Literature Review

Transfusion in Neonates

A statement issued at the National Institute of Health Consensus Development Conference in June 1988 made the following observation: "Transfusion is a life-saving measure in the management of a variety of medical and surgical conditions...For many patients, homologous red cell transfusion carries great benefits, permitting surgical procedures that would not otherwise be possible, and allowing medical therapies for patients who are or may become anemic" (Stehling, 1989). In addition, transfusions are important for various populations and age groups; this is particularly true for premature infants. According to Strauss: "transfusions of blood components are indispensable to the modern care of critically ill premature infants" (Strauss, 1991). In addition, this population is among the most frequently transfused group of patients (Ringer et al, 1998). In the United States, it has been estimated that approximately 38,000 neonates with birthweights below 1500 grams are born annually and of these approximately 80% will require blood product support (Hume and Blanchette, 1995). Up to 70% of babies below 1500 grams receive at least one blood transfusion during their time in the NICU and pre-term neonates are exposed to three times the number of blood transfusions compared to infants and older children (Bruce and Roe, 1997).

However, transfusion practices for neonates are controversial, variable and based on scanty scientific information (Strauss, 1991). For the most part, no controlled scientific studies have been carried out to clearly establish the indications for transfusion of blood components in premature infants. Transfusion in neonates is complex because of the permeable blood/brain barrier, immaturity of the immune system and the metabolic processes of the liver (Davies and Kinsey, 1994).

Furthermore, the physiology of adults is very different from neonates. As such the same clinical guidelines for transfusions that are used in adults cannot be applied to small infants. Even the general indications of transfusion and normal values for hematologic parameters such as hemoglobin concentration and hematocrit levels differ between these two populations. Neonates have a slightly larger blood volume (approximately 85 ml/kg) per kilogram of body weight than adults, leading to a slightly higher dose regimen to achieve the desired post-transfusion result (McMican, 1988). Pediatric packs are utilized for infants instead of adult blood unit packs. The difference lies in the amount of blood per bag as a single unit is divided into either a quad pack (4 bags) or a quint pack (5 bags). Due to their low volume, small packs of blood must be handled correctly to avoid deterioration during storage and transport (Greaves et al, 1982).

Despite the intricacy that exists in this field, guidelines have been established for the use of blood products in infants in a variety of clinical settings such as extracorporeal membrane oxygenation (ECMO), exchange transfusion and cardiopulmonary bypass where massive amounts of blood are required (Hume and Blanchette, 1995). However, most transfusion decisions are based on the measurement of phlebotomy losses, anemia and evaluation of clinical status (Ringer et al, 1998). In some cases, the value of transfusion is clear, for instance, transfusing red blood cells to treat anemia that has caused congestive heart failure and transfusing platelets to treat severe thrombocytopenia with bleeding (Strauss, 1991). In other clinical situations, the value of a transfusion is not clear (Strauss, 1991).

Moreover, complications with blood transfusions exist in terms of transmission of infectious diseases, non-infectious transfusion reactions and vessel catheterization in infants. These risks are magnified in this special population due to their small size,

prematurity and difficulty in interpreting the infant's illness severity and vital signs. In addition, neonates also receive multiple transfusions resulting in increased donor exposure. Although transfusion of blood products is an essential and potentially life-saving measure, not all blood transfusions are beneficial to patients (Blanchette et al, 1991).

Types of Blood Products

Various kinds of blood products are used in the treatment of neonates. They include red blood cells (RBCs), fresh frozen plasma (FFP), platelets, whole blood, cryoprecipitate, granulocytes and albumin. The uses and guidelines for the administration of these blood products are briefly depicted.

Red Blood Cells (RBCs)

Premature newborns most commonly receive RBC transfusions (Ringer et al, 1998). Most infants with a birthweight of less than 1 kg do need RBC transfusions (Strauss, 1997). In 70s and early 80s, booster or 'top-up' transfusions were given to keep the hemoglobin concentration above a given level (Blank et al, 1984), to improve weight gain (Stockman et al, 1980) or to treat apnea (Kattwinkel, 1977). However, Blank and his colleagues showed that provision of booster transfusions did not contribute to weight gain and the treatment of apnea, thus their efficacy was not supported in growing premature infants who were not ill (Blank et al, 1984). The decision to transfuse erythrocytes should continue to be governed by factors associated with oxygen delivery and clinical assessments of the baby, including feeding, weight gain and cardiorespiratory status (Fetal and Newborn Committee, 1992). Although an increased

erythrocyte concentration has potential benefits (Strauss et al, 1990), RBC transfusions to infants on the basis of hemoglobin level alone cannot be justified. The clinical judgment and assessment by the physician is required.

Over the years, many specifications for the use of RBCs have been established. The current guideline given by the Red Blood Cell Administration Practice Guideline Development Task Force of the College of American Pathologists in neonates is summarized below (Simon et al, 1998). They stated that the neonatal patient should be transfused when one of the following situations occur:

- hematocrit ≤ 0.20 or hemoglobin ≤ 7 g/dl and reticulocyte count < 4%;
- hematocrit ≤ 0.25 or hemoglobin ≤ 8 g/dl and any of the following conditions:
    a) episodes of apnea/bradycardia requiring bag-mask ventilation
    b) sustained tachycardia or tachypnea
    c) cessation of adequate weight gain
    d) mild respiratory distress syndrome (RDS);
- hematocrit ≤ 0.30 or hemoglobin ≤ 10 g/dl with moderate RDS;
- hematocrit ≤ 0.35 or hemoglobin ≤ 12 g/dl with severe RDS requiring mechanical ventilation or severe congenital heart disease associated with cyanosis or heart failure;
- acute blood loss with shock due to vasa praevia, premature separation of the placenta, cord accidents and fetal-maternal transfusion causing hypovolemic shock;
- do not transfuse to replace blood removed for laboratory tests or for low hematocrit alone unless above criteria are met.

The above mentioned criteria decrease the number of transfusions required by neonates. The metabolic complications of erythrocyte transfusion include hyperkalemia associated with cardiac arrest (Fetal and Newborn Committee, 1992). However, to limit donor exposure with RBCs, units stored up to 42 days are acceptable unless hyperkalemia is a known problem (Simon et al, 1998). Most RBC transfusions performed in neonates are of small volume (5 to 15 ml of RBCs per kilogram of body weight) and are repeated frequently (Strauss et al, 1990).

It was recently shown that the number of RBC transfusions given to very low birthweight (VLBW) infants has decreased, without an apparent increase in adverse clinical outcomes (Widness et al, 1996). In addition, there is some evidence to suggest that even the number of donors to whom pre-term infants are exposed is declining (Hume and Blanchette, 1995). These changes in RBC transfusion practices can be attributed to the combined effects of the provision of sophisticated care, noninvasive monitoring techniques, surfactant therapy, and more conservative transfusion policies. Developments in erythropoietin therapy may further decrease the requirement of RBC transfusions.

Fresh Frozen Plasma (FFP)

Transfusions of fresh frozen plasma in newborn infants merit special consideration, as it is the second most commonly used product in the NICU after RBCs. FFP contains high levels of coagulation factors such as factor 5 and FVIII, naturally occurring anticoagulant factors and opsonins (Chalmer and Gibson, 1994). There is evidence that fresh frozen plasma may enhance neonatal neutrophil chemotaxis (Eisenfeld et al, 1992).

The criteria for transfusion of FFP are summarized below (Blanchette et al, 1991):

- bleeding, or an invasive procedure, in a patient with a coagulation factor deficiency due to vitamin K deficiency, liver disease, sepsis complicated by disseminated intravascular coagulation (DIC) or inherited factor deficiencies (Hathaway, 1975) or a markedly prolonged prothrombin, and/or partial thromboplastin times;
- replacement therapy in anti-thrombin III or protein C or S deficiencies;
- replacement therapy during therapeutic plasma exchange for disorders in which FFP is beneficial.

The average neonatal dose for FFP is 10 to 20 ml/kg of body weight. Type AB FFP is often used for neonatal transfusion because a single unit will be ABO compatible with the red blood cells of all infants (Schmidt, 1987). FFP should not be used for the correction of hypovolemia alone (Blanchette et al, 1991), 'formula replacement' or nutritional support or to adjust the hematocrit of red cell concentrates prior to transfusion as this causes double donor exposure (Chalmer and Gibson, 1994).

Platelets

Platelet transfusions are indicated for support of children with clinically important quantitative and/or qualitative platelet disorder (Blanchette et al, 1991). The criteria for the infusion of platelet concentrates are as follows (Blanchette et al, 1991):

- Premature infants (gestational age < 37 weeks)
    a) blood platelets < 50 x 10^9/L in a stable infant
    b) blood platelets < 100 x 10^9/L in a sick infant;
- All other infants
    a) blood platelet count < 20 x 10^9/L in a patient with failure of platelet production

b) blood platelet count < 50 x 10^9/L with active bleeding or the need for an invasive procedure in a patient with failure of platelet production

c) blood platelet count < 100 x 10^9/L with active bleeding plus DIC or other coagulation abnormalities

d) bleeding with a qualitative platelet defect and significant prolongation of the bleeding time regardless of platelet count

e) cardiovascular bypass surgery with unexplained excessive bleeding regardless of platelet count.

The dose of platelets required in neonates is 10 ml/kg. These concentrates should be transfused as rapidly as the neonate's overall condition permits, certainly within two hours (Blanchette et al, 1991). When platelets are transfused, the longest survival is with those that are matched for ABO (Davies and Kinsey, 1994). The above criteria are applied mostly to quantitative platelet disorders. Another platelet disorder most frequently experienced by neonates is qualitative and called thrombocytopenia. The reasons for this disorder in infants are multi-factorial ranging from feto-maternal incompatibility for a platelet antigen (Blanchette, 1988), disseminated intravascular coagulation (Letsky, 1990), infection, sepsis, immunologic destruction (McMican, 1988), congenital viral disease of the TORCH group (Toxoplasmosis, Rubella, Cytomegaloviurs and Herpes virus) (Sacher et al, 1989) and birth asphyxia (Blanchette et al, 1995). The risk of life-threatening hemorrhage, particularly intracranial hemorrhage, relates to the severity of thrombocytopenia (Blanchette et al, 1991). In all thrombocytopenic situations, it is important to avoid possible drugs that impair platelet function (e. g. aspirin) and the use of intramuscular injection (Davies and Kinsey, 1994).

Whole Blood

Whole blood or reconstituted whole blood supplies all the coagulation factors and plasma proteins that are needed in neonates. Reconstituted whole blood is prepared by re-suspending red cell concentrates, often after washing, in FFP (Sacher et al, 1989). Reconstituted whole blood is commonly used because it obviates the need for fresh blood and concerns about the high plasma potassium and low pH present in stored whole blood (Sacher et al, 1989). The following guidelines have been proposed for the use of whole blood in neonates (Blanchette et al, 1991):

- massive transfusion or acute blood loss (> 1 blood volume estimated as 70 ml/kg of body weight in 24 hours);
- exchange transfusion;
- cardiovascular bypass surgery;
- extracorporeal membrane oxygenation.

Cryoprecipitate

Cryoprecipitate is rich in four of the proteins required for hemostasis: anti-hemophilic factor (VIII), fibrinogen, fibronectin and factor XIII (McMican, 1988). Cryoprecipitate is often used when there is bleeding or an invasive procedure (Blanchette et al, 1991). Additional use is indicated in neonates who have congenital coagulation factor deficiencies or anomalies, including hemophilia A, dysfibrinogenemia, and von Willebrand's disease (Snyder, 1983) and acquired hypofibrinogenemia associated with DIC (Chalmer and Gibson, 1994). DIC may require FFP supplemented with cryoprecipitate if there is evidence of severe consumptive state with fibrinogen depletion (Hume and Bard, 1995). The suitable starting dose for cryoprecipitate is 10 ml/kg.

Granulocytes

During the first week of life, healthy neonates exhibit both neutrophilia and neutrophil functional abnormalities (Strauss, 1988). The criteria for the transfusion of granulocytes are given below (Blanchette et al, 1991):

- bacterial sepsis in neonates < 2 weeks of age with neutrophil plus band cell counts < 3×10^9/L;
- bacterial sepsis unresponsive to antibiotics in patients > 2 weeks of age with neutrophil plus band cell counts < 0.5×10^9/L;
- documented infection(s) unresponsive to antibiotics plus a qualitative neutrophil defect, regardless of the neutrophil plus band cell count.

The average volume transfused for granulocytes is 10 to 15 ml/kg of body weight in the neonate (McMican, 1988). These transfusions should be continued daily until either the infection resolves or the blood neutrophil count rises to greater than 0.5×10^9/L (Blanchette et al, 1991). In addition, transfusions of granulocytes should be infused promptly within a few hours of donation (Strauss, 1991).

Granulocyte transfusion has a very limited role worldwide due to (Davies and Kinsey, 1994):

- short circulatory survival time of transfused granulocytes;
- activation of granulocytes during collection;
- technical and financial problems in producing granulocyte concentrates in adequate doses.

In addition to granulocytes, intravenous immunoglobulin (IVIG) is administered in neonates, which is prepared from unselected donor plasma and contains the full spectrum of antibodies present in the normal donor population (Chalmer and Gibson, 1994). The major indication for IVIG is replacement therapy in primary hypogammaglobulinemia, secondary immunodeficiency states and a number of immunological disorders where IVIG appears to act as an immune modulator (Chalmer and Gibson, 1994). However, IVIG is expensive and has only a small number of clearly established indications.

Albumin

Albumin is available in both 5% and 25% solutions and is prepared from large pools of human plasma (Chalmer and Gibson, 1994). The criteria for the transfusion of albumin are given below (Blanchette et al, 1991):

- acute correction of hypoalbuminemia when clinically indicated in the treatment of fluid overload;
- correction of hypovolemia when colloid infusion is indicated;
- replacement therapy for fluids in therapeutic plasma exchange procedures with normal saline.

Albumin at 5% is often used in the delivery room to resuscitate neonates in shock who are presumed to have had an episode of acute blood loss (Letsky, 1990). Its use is justified because the baby's blood group is not yet known and it is necessary to give optimum treatment promptly with the least hazard (Letsky, 1990). However, albumin preparation is expensive and its place in the overall care of the sick preterm infants remains to be clarified (Chalmer and Gibson, 1994).

Unit and Donor Exposure in Neonates

Unit exposure refers to the number of transfusions received while donor exposure refers to the number of donors the recipient is exposed to while being transfused. Since neonates require relatively large amounts of blood in small units they are at risk of receiving multiple transfusions and being exposed to numerous donors. As a result, many strategies have been proposed and implemented to reduce both unit and donor exposure in this population.

Some strategies that have been successful in reducing unit exposures include:

- Increasing the red blood cell mass through placental transfusion by delayed cord clamping in the delivery room (Kinmond et al, 1993). However, this must be weighed against the possible increase in systemic arterial pressure that might result in intraventricular hemorrhage (Hofmeyer et al, 1988).
- A promising intervention in preterm infants is the use of recombinant human erythropoietin, which has been shown to safely stimulate erythropoiesis (Paul et al, 1997).
- Prenatal steroid therapy, surfactants, and improved ventilator therapies have also contributed to less phlebotomy loss (Strauss, 1995).
- Noninvasive procedures to assess hematologic parameters, as the amount of RBCs transfused to neonates is directly related to phlebotomy losses (Shannon et al, 1995).

For neonates, it has been traditional to use fresh blood (< seven days) (Scanlon and Krakaur, 1980) but this has given rise to high donor exposure, typically up to eight to 10 different donors (Strauss et al, 1990). The strategies for reducing donor exposure are

numerous and quite different from those for reducing transfusion requirements. Some of these approaches are outlined below:

- Prolonging the acceptable age of blood for simple iatrogenic phlebotomy replacement (Donowitz et al, 1989).
- Use of a sterile connecting device to withdraw just what is needed per transfusion so that it is possible to create many small volume transfusions from a single unit (Donowitz et al, 1989).
- The use of quadruple packs for individual patients to minimize donor exposures for multiple transfusions without blood wastage (Donowitz et al, 1989).
- A strategy under review is to recover unused autologous red cells from laboratory blood samples and to prepare them for infusion (Balin et al, 1989).
- The intra- and post-operative collection, processing and re-infusion of shed red blood cells is also being explored (Billman, 1993).

In addition to these strategies, innovations and proposed guidelines for transfusion practices have increased the safety of the blood supply. All homologous blood products pose risks, although very small to the recipient. Risk reduction strategies are optimally effective only when the transfusion service, the attending physician, and the patient are all participants (Billman, 1993). The best approach now is to transfuse blood components only when they are highly likely to benefit the neonate (Strauss, 1991).

Changes in Transfusion Practices

Due to technological advances and implementation of proper transfusion guidelines the number of units received and the number of donors that an infant is exposed to has

decreased in recent years. Moreover, screening of most of the blood products for infectious diseases such as human immunodeficiency virus (HIV-1 and HIV-2) and hepatitis C virus (HCV) has further increased the safety of the blood supply. Since November, 1985 Canada's donor blood supply has been screened for antibodies to HIV and since 1990 routine screening for antibodies to HCV has been performed (Heddle et al, 1997). Laboratory testing is also performed to detect hepatitis B, syphilis, and retrovirus (human T-cell leukemia/lymphoma virus type II and I) infections in the donor blood supply (Strauss, 1991). It has been estimated that the current risk of an infected donor not being detected is about one in 1 million (Strauss, 1990). Because the exact figure is unknown, some controversy exists, and most experts accept a rate between one and 20 per million (Strauss, 1991). Canada and many other countries have launched information campaigns suggesting that patients who were admitted to hospital and received a blood transfusion between 1978 and 1985 should be tested for HIV and that patients who received transfusions between 1978 and 1990 should be tested for HCV (Heddle et al, 1997).

Procedures for screening the donor blood supply have also had an effect on transfusion practices. A retrospective study conducted at the University of Iowa Hospitals and clinics, reviewed blood bank and hospital records for a 12-year period to determine changes in the pattern of RBC transfusions given to very low-birthweight (VLBW) infants (Widness et al, 1996). Three study years were selected namely 1982, 1989 and 1993 to encompass major events such as widespread awareness of HIV, use of technological advances such as surfactant therapy as well as antenatal steroid therapy for mothers of preterm infants and initiation of uniform RBC transfusion guidelines for neonates, respectively. The results showed a significant decrease in the percentage of infants who

received transfusion of RBCs ($p = 0.006$) and the number of RBC transfusions given to each infant ($p < 0.0001$) for the selected years (Widness et al, 1996).

Mortality and Survival in Neonates

Receipt of a blood transfusion can be used as a descriptive epidemiologic index of morbidity in the general population as it is independently predictive of mortality, adding to the predictive value of age, gender and previous hospitalization (Vamvakas and Taswell, 1994). Vamvakas and Taswell conducted a study in adults and found an association of transfusion with both long-term morbidity and mortality and current illness severity (Vamvakas and Taswell, 1994). They hypothesized that transfusion per se might contribute to the observed increased morbidity and mortality rates (Vamvakas and Taswell, 1994). This may be true for adults and older children, however, for neonates both the need for a transfusion and mortality are related to birthweight, gestational age and underlying illness severity (Malaysian Very Low Birth Weight Study Group, 1997) (Paul et al, 1997; Brown et al, 1990).

Most infant deaths occur in the neonatal period, with the majority associated with low birthweight (Luban, 1991). However, there has been only one nationwide prospective observational study of outcome of all very low birthweight (VLBW) infants admitted to the NICU in Malaysia between January 1, 1993 and June 30, 1993. This study showed that the risk factors significantly associated with increased mortality before discharge were lower birthweight and gestational age while lower risk of mortality was associated with blood transfusions (Malaysian Very Low Birth Weight Study Group, 1997). A recent study has also shown that at any given gestational age, infants with low birthweight have

relatively high morbidity and mortality (McIntire et al, 1999). Strict transfusion guidelines that were applied in a study by Alagappan and colleagues in low birthweight infants showed that the transfusion guidelines did not affect growth rate or overall mortality (Alagappan et al, 1998).

Vamvakas and Taswell performed a Kaplan-Meier survival analysis and established a dose-response relationship between the amount of blood components received and a reduction in the subsequent length of survival for adults (Vamvakas and Taswell, 1994). Shorter survival after a blood transfusion was correlated with male gender, greater age, receipt of blood components for treatment of a medical disease as opposed to surgery, receipt of platelets, FFP or more than 10 units of RBCs (Vamvakas and Taswell, 1994). These types of studies in neonates would be of great consequence as this population is the most frequently transfused but research in terms of survival has never been performed. Mortality and survival in neonates is likely to be quite different than in adults and is possibly associated with different risk factors.

Hepatitis C in Neonates

Hepatitis C virus (HCV) has been shown to be the most common cause of post-transfusion hepatitis (Khalifa et al, 1993). In the pediatric population, hepatitis C infection is most likely to be found in recipients of blood and blood products and infants born in high risk situations (A-Kader and Balistreri, 1993). In a general look-back study conducted at the Hospital for Sick Children in Toronto for the time period December 1985 to May 1990, severe illnesses such as congenital heart disease, neoplasia and prematurity requiring a brief, but often intensive period of transfusion were associated

with HCV (Roberts et al, 1998). Another study performed by Bortolotti and his associates, showed that 60% of infected HCV children had received blood transfusions in the perinatal period (Bortolotti et al, 1994).

The incidence of transfusion-acquired hepatitis C virus infection has declined markedly in Canada over the past 15 years (Preiksaitis et al, 1998). Important to the declining risk of post-transfusion hepatitis, is the reduced prevalence of HCV seropositivity in blood donor pools (Dodd, 1990), likely the result of tighter donor screening criteria (Birkmeyer et al, 1992). Moreover, the introduction of first-generation and second-generation anti-HCV assays along with polymerase chain reaction (PCR) to identify HCV-RNA for screening blood and blood products has dramatically decreased the incidence of HCV in the blood supply. However, the rate of transfusion-associated hepatitis has not been determined accurately in infants (Strauss, 1991).

There are few published data regarding the natural history or associated conditions of HCV infection in children (Bortolotti et al, 1993). However, it is probable that the risk of becoming a chronic carrier is as high in this age group as in adult patients (50% to 75%) (Alter et al, 1992). Disorders leading to long-term morbidity (e. g. post-hepatic cirrhosis and hepatic cancer) are particularly serious when they occur during infancy because of the potential for extended disability requiring costly care (Strauss, 1991). In addition, HCV infected infants are theoretically at somewhat elevated risk of developing severe liver disease two to three decades later, although this still needs to be investigated (Delage, 1995). In the study conducted by Bortolotti and associates, histologically, severe hepatitis and cirrhosis seem to be an infrequent feature of chronic HCV infection in childhood and adolescence, in spite of persistent chronic hepatitis (Bortolotti et al, 1994).

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Chapter 3

Methods

Data Collection

The charts of the University of Alberta Neonatal Intensive Care Unit (NICU) were extracted manually and by microfilm for the period of January 1978 to April 1992 from the Department of Medical Records. Charts for 1982 and 1983 were not included. Due to administrative problems, most of the records were either missing or destroyed.

The following sheets were extracted from the patient charts for the thirteen years and the two groups of infants.

- For transfused infants: Admission sheet, discharge summary, transfer sheet (if applicable), chart transfusion sheet and subsequent NICU admission sheet (if applicable) were obtained.
- For non-transfused infants: Admission sheet, discharge summary (final diagnoses written or a photocopied sheet) and subsequent NICU admission sheet (if applicable) were the only requirements.

From these patient charts, birthweight in grams, gestational age in weeks and transfusion status (yes/no) was obtained from the discharge summary. Gender and length of stay in days for the University of Alberta NICU was present on the admission sheet. If there was evidence of a subsequent NICU admission length of stay in days, transfusion status and any details of transfusion administrations were entered in the same record. For all transfused infants, details on the type of blood product (RBC, FFP, platelets, whole blood, cryoprecipitate, white blood cells [WBC], albumin and intravenous immunoglobulin [IVIG]), number of transfusions received and donor identification number were abstracted from the chart transfusion sheet.

Information on death during follow-up was obtained on a regular basis from medical files, Provincial vital statistics and the Alberta Health Care Insurance Plan. Patients who were discharged alive from the NICU were followed until November 1998. Information pertaining to the date of death was collected from medical charts. However, the cause of death for the patient was not recorded.

A unique identifier was given to each infant. Duplicate charts are charts that have been repeated for the same infant. They were identified from the logbook or by reviewing the infant's name and birth date. If the duplicate chart was same as the chart present in the database, it was not entered again. Missing charts are charts that are present in the logbook but have been misplaced or missing in the Department of Medical Records. There were 53 missing charts and were not entered. All of this pertinent information was entered in a Paradox 3.0 database.

The data were then converted into a dBase IV file where unit exposures (number of units received) and donor exposures (number of donors an infant was exposed to) were calculated for each infant.

Statistical Analyses

The dBase IV files were then transferred into the Statistical Package for Social Sciences (SPSS) for statistical analyses. Frequency distributions, bar charts and cross-tabs were used to describe the population in terms of demographics, hospitalization characteristics, types of blood products given, unit exposures and donor exposures. These analyses were repeated for each year from 1978 to 1992 and by year for infants who weighed less

than or equal to 1500 grams and those who weighed more than 1500 grams. For the bivariate analysis of mortality, continuous independent variables were categorized as follows: birthweight (grams; 0 to 500, 501 to 750, 751 to 1000, 1001 to 1500, 1501 to 2500, 2501 to 4500 and 4501 or higher), gestational age (weeks; 20 to 23, 24 to 28, 29 to 32, 33 to 36, 37 to 42 and 43 or higher), unit exposures and donor exposures (divided into 1, 2 to 4, 5 to10, 11 to 49 and greater than or equal to 50 units/donors). Odds ratios and 95% confidence intervals were computed using contingency table analysis as well as logistic regression. Significance levels were set at $\alpha = 0.05$ (two-tailed).

Comparison of the mean number of unit exposures for all blood products excluding albumin and IVIG as well as albumin alone was carried out using one-way analysis of variance (ANOVA) with a statistical significance level set at $\alpha = 0.05$. This calculation was carried out for the categorical independent risk factors of birthweight, gestational age, gender, death during follow-up, in hospital mortality and length of stay.

The Kaplan-Meier product-limit method was used to calculate the length of in-hospital survival with the end-point of interest being mortality in the University of Alberta NICU. The same categories were used for the variables mentioned above except for birthweight, which was further divided into eight categories (0-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3500, 3501-4500 and $\geq$ 4501). In addition, a Cox proportional-hazard regression model was created to determine the risk factors related to mortality with length of stay in days for the continuous independent variables of birthweight (grams), gestational age (weeks) and transfusion status (yes/no).

To describe the changes in transfusion practices from January 1978 to April 1992 (not including 1982 and 1983) bar and line charts were used. Bar charts were use to describe the trend for the percentage of infants who were transfused during this time period. The percentage of units used during this time period was determined by dividing the number of units for individual blood products such as whole blood, platelets, fresh frozen plasma (FFP) and packed cells (PC) and albumin over the total number of units of all blood products except IVIG. These percentages were then plotted in a line chart.

To evaluate the trend in unit exposures and donor exposures for individual blood products such as cryoprecipitate, whole blood, platelets, FFP, PC and the category including "any blood products except albumin and IVIG", donor exposures for each individual infant was divided by its corresponding unit exposures. A sum of all these values were obtained for all the infants in a particular year and means and standard deviations were computed. These values were plotted for each year.

Prevalence of hepatitis C in the general population was obtained from the report of the expert panel on hepatitis C (unpublished) conducted by Health Canada in 1998 (Hepatitis C Working Group, 1998). The unit exposure risk for HCV in the neonatal population was calculated by multiplying the prevalence of each year with the numeric unit exposures of each individual infant who was transfused. A sum of all the individual unit exposures was computed for each year and mean ± standard deviations of unit exposure risk were calculated. The number of infants likely to be infected with hepatitis C was obtained by multiplying the mean unit exposure risk in a particular year by the number of infants transfused with "any of the blood products except albumin and IVIG". In addition, survival estimates for the infants were obtained from the Kaplan-Meier

survival curves for each year and number of infected infants surviving was calculated by multiplying the survival estimates with the number of infants who were transfused with "any of the blood products except albumin and IVIG". Ranges were computed for the number of infants that are likely to have been infected with HCV and the number of surviving infants infected likely to have been infected with HCV using standard deviations for each of the estimates.

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Chapter 4

Mortality among Neonates in the University of Alberta, Neonatal Intensive Care Unit (NICU) from January 1978 to April 1992: Relationship to birthweight, gestational age and transfusion

Introduction

Neonates are among the most frequently transfused group of patients (Ringer et al, 1998). It has been estimated that approximately 300,000 neonates undergo transfusions annually in the United States (Strauss, 1991). Moreover, up to 70% of babies below 1500 grams receive at least one blood transfusion during their time in the Neonatal Intensive Care Unit (NICU) (Bruce and Roe, 1997). Pre-term neonates are exposed to 3 times the number of blood transfusions compared to infants and older children (Bruce and Roe, 1997). Strauss reported that infants with birthweights less than 1500 grams received an average of 10 transfusions (Strauss, 1991). Previous studies have shown gestational age less than 30 weeks to be most predictive of the need for two or more transfusions (Brown et al, 1990). Other reports (Kilbride et al, 1988; Cook et al, 1993; Liu et al, 1994; Wang-Rodriguez et al, 1996) suggest that, among premature infants, those who are larger and with longer gestation will require less transfusion support than smaller and more premature infants. Thus, relationships between transfusions, birthweight and gestational age have been established.

The relationship between mortality, transfusion, birthweight and gestational age has not been explored in neonates. On the other hand, Vamvakas and Taswell have shown an association of transfusion with both long-term morbidity and mortality suggesting that transfusion per se could contribute to the increased morbidity and mortality rates observed in critically ill adult populations (Vamvakas and Taswell, 1994). Their study did not provide any evidence that the observed association could be causal but they stated its possibility. Since neonates and adults are different in terms of illness severity, size and physiology, the results from the study of adults may not be applicable to neonates. In addition, for neonates, the physiologic basis for transfusion decisions is particularly

limited and controversy persists regarding the indications and benefits of transfusion therapy (Ringer et al, 1998). Transfusion practices in adults are less controversial as there have been more systematic studies of transfusion-associated complications in adults compared to neonates (Holman et al, 1995). Thus, birthweight and gestational age may affect mortality and transfusion requirements in neonates in the same manner or differently. Birthweight and gestational age can be predictors for transfusion need and also affect mortality risk.

This paper reports the results of a descriptive retrospective cohort study examining the relationship between neonatal mortality and birthweight, gestational age and transfusion at a University of Alberta NICU from the period January 1978 to April, 1992 (not including the years of 1982 and 1983).

Methods

Data Collection and Study Population

Neonatal patient charts were extracted for the years January 1978 to April 1992. The years 1982 and 1983 were not included in this study because the charts for these two years were either missing or destroyed. During this time, 7,993 infants were admitted to the NICU and their charts were examined. Information on the following variables was collected:

1) birthweight in grams, gestational age in weeks, in-hospital mortality and transfusion status (Yes/No), per the discharge summary;
2) gender and death during follow-up from the admission sheet, subsequent admission sheet and/or medical records tandem checks;

3) blood components received and number of transfusions administered from the chart transfusion sheets.

Information on death during follow-up was obtained on a regular basis from medical files, Provincial vital statistics and the Alberta Health Care Insurance Plan. Patients who were discharged alive from the NICU were followed until November 1998. Information pertaining to the date of death was collected from medical charts. However, the cause of death for the patient was not recorded. Complete information was available for 7,978 infants. Of the 15 records, 11 were missing gestational age while four were missing birthweights. There were 49 re-admissions to the NICU.

Statistical Analysis

Odds ratios, 95% confidence intervals and p-values were computed using standard contingency table methods for the relationship between mortality and birthweight, gestational age, gender, transfusion status and unit intervals for individual and grouped blood products. For birthweight, 1501 to 2500 grams was used as the reference category. Although the birthweights of these babies would usually be considered low, their mortality was less than that of the larger babies. This suggests that babies with normal birthweights who are admitted tot he NICU are more likely to have serious medical conditions other than problems usually associated with prematurity. A similar rationale was used in defining 33 to 36 weeks as the reference category for gestational age. Non-transfused infants were a reference category for the bivariate analysis of unit intervals and mortality.

One-way Analysis of Variance (ANOVA) was used to compare the average number of unit exposures for all blood products excluding albumin and albumin alone for each independent categorical risk factor. Significance levels were established at $\alpha = 0.05$ (two-sided).

Results

Approximately half of all neonates were in the normal range for birthweight (2501 to 4500 grams) and 46.6% of infants were in the normal range gestational age (37 to 42 weeks) (Table 4-1). There were more males (58%) than females (42%).

Sixteen percent of the infants were in the very low birthweight (VLBW) category (< 1500 grams) while 22.4% were pre-term (< 32 weeks). There were relatively fewer overweight and overdue babies: 1.3% and 0.6% respectively (Table 4-1). The mean ± SD for birthweight and gestational age was 2530 ± 959 grams and 36 ± 4 weeks, respectively.

Overall, 46.2% of the neonates were transfused (Table 4-2). Most of the deaths occurred in the hospital (764 of 892). The overall mortality rate was 11.2% with 9.5% dying during the initial NICU admission. Overall survival of these infants was 88.8%.

For the bivariate analysis (Table 4-3), the highest risk group for mortality was in the lowest gestational age interval (20-23 weeks) with an odds ratio of 280.0 (95% CI: 66.6, 1176.8). For infants weighing, less than 500 grams the odds ratio for mortality was 121.3 (95% CI: 42.4, 347.1).

Table 4-1: Description of neonatal patients

Characteristics	n	%
Birthweight (grams)		
0 – 500	36	0.5
501 - 750	150	1.9
751 – 1000	299	3.7
1001 – 1500	819	10.3
1501 – 2500	2619	32.8
2501 – 4500	3964	49.6
≥ 4501	102	1.3
Total	7989	100
Gestational age (weeks)		
20 – 23	36	0.5
24 – 28	566	7.1
29 – 32	1185	14.8
33 – 36	2432	30.5
37 – 42	3718	46.6
≥ 43	45	0.6
Total	7982	100
Gender		
Male	4633	58.0
Female	3360	42.0
Total	7993	100

VLBW infants (0-500, 501-750, 751-1000 and 1001-1500 grams) had significantly elevated odds ratios (121.3, 29.4, 9.9 and 2.6, respectively). This was also true for pre-

Table 4-2: Hospitalization characteristics of the neonatal patient population

Characteristics	n	%
Transfusion status		
Transfused	3692	46.2
Non- transfused	4301	53.8
Total	7993	100
Overall mortality		
Died	892	11.2
Survived	7101	88.8
Total	7993	100
In-hospital mortality		
Died	764*	9.5
Survived	7229	90.5
Total	7993	100

* 8 of these deaths occurred during the second admission to the NICU

term infants (20-23, 24-28 and 29-32 weeks) with odds ratios of 280.0, 11.8 and 1.7, respectively.

Mortality for infants who would usually be considered normal for birthweight (2501-4500 grams) and gestational age (37-42 weeks) were at significantly higher risk for mortality compared to the reference categories (OR = 1.5, 95% CI: 1.2, 1.8 and OR = 1.8, 95% CI: 1.5, 2.2 respectively). Overweight and overdue babies have risk factors that did not differ significantly from the reference category.

Table 4-3: Comparison of those who died during follow-up with those who survived for selected risk factors

Characteristics	Died		Survived		Odds ratio	95% confidence interval	p-value
	n	%	n	%			
Birthweight (grams)							
0 – 500	32	88.9	4	11.1	121.3	42.4, 347.1	< 0.0001
501 – 750	99	66.0	51	34.0	29.4	20.3, 42.7	< 0.0001
751 – 1000	118	39.5	181	60.5	9.9	7.5, 13.1	< 0.0001
1001 – 1500	119	14.5	700	85.5	2.6	2.0, 3.3	< 0.0001
1501 – 2500	162	6.2	2457	93.8	1.0	Reference category	
2501 – 4500	356	9.0	3608	91.0	1.5	1.2, 1.8	< 0.0001
≥ 4501	5	4.9	97	95.1	0.8	0.3, 1.9	0.60
Gestational age (weeks)							
20 – 23	34	94.4	2	5.6	280.0	66.6, 1176.8	< 0.0001
24 – 28	236	41.7	330	58.3	11.8	9.3, 15.0	< 0.0001
29 – 32	113	9.5	1072	90.5	1.7	1.3, 2.3	< 0.0001
33 – 36	139	5.7	2293	94.3	1.0	Reference category	
37 – 42	362	9.7	3356	90.3	1.8	1.5, 2.2	< 0.0001
≥ 43	5	11.1	40	88.9	2.1	0.8, 5.3	0.13
Gender							
Female	409	12.2	2951	87.8	1.2	1.0, 1.4	0.014
Male	483	10.4	4150	89.6	1.0	Reference category	
Transfusion							
Transfused	673	18.2	3019	81.8	4.2	3.5, 4.9	< 0.0001
Non-transfused	219	5.1	4082	94.9	1.0	Reference category	

Infants who were transfused had a four-fold higher risk of mortality than non-transfused infants (OR = 4.2, 95% CI: 3.5, 4.9). Mortality was slightly but significantly higher for female patients than males.

For the category "any blood products except albumin and IVIG" and the individual blood products all of the odds ratios for mortality in terms of unit exposures were significantly different from the reference category of non-transfused infants (Table 4-4). In general, mortality increased with increasing unit exposures for each category. The odds ratio for 50 or more units of packed cells was not calculated due to small numbers.

Comparison of the mean number of transfusions for the category of "any blood products except for albumin and IVIG" shows that VLBW infants on average received more of these blood products than those in the other birthweight categories. The highest mean numbers of transfusions were in the 501-750 gram, 751-1000 gram and 1001-1500 gram categories (Table 4-5). A similar pattern was seen for gestational age, although for gestational age the lowest category (20-23 weeks) had relatively high mean numbers of transfusions. For gender, the difference in the mean number of transfusions was not significant. On average the neonates who died received more transfusions compared to the neonates who survived.

In general, the patterns for the number of transfusions with albumin paralleled the results for the category "any blood product except albumin and IVIG".

Table 4-4: Comparison of those who died during follow-up with those who survived for selected blood products

Unit exposure for selected blood products	Died		Survived		Odds ratio	95% confidence interval	p – value
	n	%	n	%			
Non-transfused	219	2.7	4082	51.1	1.0	Reference category	
Fresh Frozen Plasma (FFP)							
1	147	33.0	601	42.4	4.6	3.6, 5.7	< 0.0001
2 – 4	173	38.9	477	33.7	6.8	5.4, 8.4	< 0.0001
5 – 10	75	16.9	252	17.8	5.5	4.1, 7.4	< 0.0001
11 – 49	47	10.6	85	6.0	10.3	7.0, 15.1	< 0.0001
50 and higher	3	0.7	1	0.1	55.9	5.8, 539.6	0.0005
Total	445	100	1416	100			
Packed Cells (PC)	593	26.1	2275	73.9			
1	165	27.8	837	36.8	3.7	3.0, 4.6	< 0.0001
2 – 4	219	36.9	940	41.3	4.4	3.6, 5.3	< 0.0001
5 – 10	123	20.7	350	15.4	6.6	5.1, 8.4	< 0.0001
11 – 49	85	14.3	148	6.5	10.7	8.0, 14.5	< 0.0001
50 and higher	1	0.2	0	-		Not calculated	
Total	593	100	2275	100			
Any blood products except albumin and IVIG*							
1	115	17.9	817	30.8	2.6	2.1, 3.3	< 0.0001
2 – 4	205	31.8	985	37.1	3.9	3.2, 4.8	< 0.0001
5 – 10	150	23.3	505	19.0	5.6	4.4, 7.0	< 0.0001
11 – 49	163	25.3	335	12.6	9.1	7.2, 11.5	< 0.0001
50 and higher	11	1.7	11	0.4	18.7	8.0, 43.6	< 0.0001
Total	644	100	2653	100			
Albumin							
1	80	33.5	319	36.8	3.1	2.3, 4.3	< 0.0001
2 – 4	61	25.5	362	41.7	4.6	3.5, 6.1	< 0.0001
5 – 10	64	26.8	145	16.7	8.2	6.0, 11.4	< 0.0001
11 – 49	34	14.2	42	4.8	15.1	9.4, 24.2	< 0.0001
Total	239	100	868	100			

* Includes white blood cells (WBCs), cryoprecipitate, whole blood, platelets, fresh frozen plasma and packed cells.

Table 4-5: Comparison of the mean number of transfusions given for "any blood products except albumin and IVIG" and albumin for selected risk factors

Characteristics	Any blood products except albumin and IVIG Mean ± SD	Albumin Mean ± SD
Birthweight (grams)*		
0 – 500	3.8 ± 2.0	5.0 ± 2.8
501 – 750	12.9 ± 15.0	8.1 ± 8.6
751 – 1000	11.3 ± 10.7	5.5 ± 5.7
1001 – 1500	7.5 ± 8.7	4.0 ± 4.6
1501 – 2500	4.6 ± 8.5	3.2 ± 4.3
2501 – 4500	4.9 ± 8.4	3.2 ± 3.5
≥ 4501	3.6 ± 3.3	4.7 ± 3.7
Gestational age (weeks)*		
20 – 23	9.4 ± 13.1	9.8 ± 10.8
24 – 28	10.7 ± 11.8	6.0 ± 6.4
29 – 32	6.4 ± 7.8	3.1 ± 3.5
33 – 36	4.2 ± 7.4	3.4 ± 4.2
37 – 42	5.2 ± 9.6	3.2 ± 3.9
≥ 43	3.0 ± 2.3	3.8 ± 2.7
Gender^		
Female	5.8 ± 8.6	4.1 ± 5.0
Male	6.2 ± 9.7	3.7 ± 4.6
Overall mortality*		
Died	9.2 ± 14.0	5.7 ± 6.5
Survived	5.3 ± 7.5	3.3 ± 4.0
In-hospital mortality*		
Died	9.2 ± 14.1	6.0 ± 6.8
Survived	5.4 ± 7.9	3.3 ± 4.0

* $p = <0.001$

^ $p = 0.226$ for "any blood products except albumin and IVIG" and 0.193 for albumin

Discussion

The purpose of this study was to describe the relationship between mortality and birthweight, gestational age, and transfusions in neonates. In-hospital mortality was 9.5% and approximately half of the patients were transfused.

Previous studies of NICU populations have typically included only VLBW or pre-term infants (Paul et al, 1997; Ringer et al, 1998; Brown et al, 1990). Almost half of the infants that were admitted to the NICU fell into the normal range for birthweight and gestational age. These infants probably had other significant underlying diseases that required admission to the NICU. Only 16.2% of the patients would have been classified as VLBW and 22.4% as pre-term.

Elevated mortality was found for infants who weighed less than 1500 grams, were younger than 29 weeks and who were transfused. The Malaysian Very Low Birth Weight Study Group found similar results. A stepwise logistic regression found that mortality was associated with low gestational age and low birthweight. An increase of one week for gestational age carried an odds ratio of 0.7 (95% CI: 0.65, 0.8; $p < 0.0000$). For birthweight, every 100 gram increment had an odds ratio of 0.6 (95% CI: 0.5, 0.7, $p < 0.0000$) (Malaysian Very Low Birth Weight Study Group, 1997).

In the present study, bivariate analyses were conducted to obtain odds ratios for various risk factors in relation to mortality. A logistic regression analysis was not performed (as in the Malaysian study) because it was felt that any multivariate analysis should consider length of stay.

However, the results differed in terms of blood transfusion status. In the Malaysian study, a lower risk of mortality was found for blood transfusions with an odds ratio of 0.4 (95% CI: 0.2, 0.7) (Malaysian Very Low Birth Weight Study Group, 1997). In the present study transfusion status was associated with a considerably higher risk of mortality, with an odds ratio of 4.2. However, the Malaysian study looked only at VLBW and pre-term infants. The fact that a transfusion could be administered implied that the infant survived long enough for the procedure to be initiated. In contrast, the present study included all infants admitted to the NICU. The reason, for receiving a transfusion in this study was not only influenced by the size and prematurity of the infant but underlying diseases that may have required transfusions such as intraventricular or intracranial hemorrhages, necrotizing enterocolitis, congenital heart disease and many others. These underlying diseases may have affected mortality in neonates with normal birthweight and gestational age as well as their smaller and younger counterparts. Further studies that incorporate diagnostic data (not available in this study) may clarify this relationship. In addition, it should be noted that the University of Alberta NICU is a referral center for northern Alberta and treats infants in need of specialized care (e.g. cardiology). The patient population may, therefore, differ from those described in other studies.

Eight types of blood products were administered in the NICU namely WBCs, cryoprecipitate, whole blood, platelets, FFP, PC, albumin and intravenous immunoglobulin (IVIG). The first six products were grouped together because they have been identified as products that transmit transfusion-associated infectious diseases. For most studies that have evaluated the various blood products, the purpose has been to determine unit and donor exposure as well as the factors that may contribute to better transfusion practices (Paul et al, 1997; Ringer et al, 1998). To our knowledge, the

effects of these blood products on mortality have not been studied in the neonatal population.

Premature newborns that are usually critically ill patients and often require blood products as part of their therapy (Ringer et al, 1998). Neonates require transfusions due to the numerous laboratory tests performed causing phlebotomy loss and to treat the physiological decline in hemoglobin levels due to prematurity or anemia (Ringer et al, 1998). In addition, Oblanden and colleagues found a strong correlation between the volume of blood drawn and the volume of blood transfused (Obladen et al, 1988). In the present study, mortality increased as unit exposure for any blood product or groups of products increased. Vamvakas and Taswell's observation of transfusion being an independent predictor of mortality for the general population maybe true for neonates as well. This is due to the dose-response relationship seen between the unit exposures of various blood products and mortality.

Estimates of transfusion-associated infectious diseases such as hepatitis C virus and HIV have been over-estimated in the past (Vamvakas and Taswell, 1994). Some possible explanations include initial over-estimate of the number of patients who received contaminated blood, lower infections rates in recipients of contaminated blood and reduced life expectancy (shorter post-transfusion survival) for urban residents (Vamvakas and Taswell, 1994). The finding that approximately 30 percent of units (5914/19905 units) were administered to babies who died suggest a possible correction factor for the neonatal population and maybe in adults as well.

Wang-Rodriguez and colleagues found that larger, older infants (> 1250 grams and > 30 weeks) received significantly fewer transfusions than younger, smaller infants (< 1250

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Wang-Rodriguez and colleagues found that larger, older infants (> 1250 grams and > 30 weeks) received significantly fewer transfusions than younger, smaller infants (< 1250 grams and < 30 weeks) with values of 2 ± 2 vs. 5 ± 2 transfusions per infant respectively, ($p = 0.0054$) (Wang-Rodriguez et al, 1996). In the present study, the average number of units that an infant was exposed to for "any blood products except for albumin and IVIG" for smaller infants (< 1500 grams) and younger infants (< 32 weeks) was considerably higher and statistically significant at 7.7 ± 7.7 and 8.8 ± 10.9 units, respectively.

The data suggest that an infant with a birthweight less than 1500 grams, younger than 29 weeks and was transfused had a higher risk of mortality. Also, significantly correlated with mortality was the number of units transfused although the mechanisms and illness severity underlying this relationship are not clear.

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Chapter 5

Mortality among Neonates as it Relates to Length of Stay in the University of Alberta Neonatal Intensive Care Unit (NICU) from January 1978 to April 1992: Relationship to Birthweight, Gestational Age and Transfusions

Introduction

To quantify the association between blood transfusion and mortality, a cohort of all residents of a United States County who underwent transfusion in 1981 was studied (Vamvakas and Taswell, 1994). They found that shorter survival after a blood transfusion was correlated with male gender, greater age, receipt of blood components for the treatment of a medical disease as opposed to surgery, receipt of platelets, fresh frozen plasma (FFP) or more than 10 units of red blood cells (RBCs). It is unclear whether these results are applicable to much younger populations.

Neonates are among the most frequently transfused group of patients, especially premature newborns who are often critically ill (Ringer et al, 1998). In the United States, it has been estimated that approximately 38,000 neonates with birthweights below 1500 grams are born annually and of these approximately 80% will require blood support (Hume and Blanchette, 1995). Nevertheless, transfusion practices for neonates are controversial, variable, and based on scanty scientific information (Strauss, 1991). Transfusion in neonates is complex because of the permeable blood/brain barrier, immaturity of the immune system and the metabolic processes of the liver (Davies and Kinsey, 1994).

Despite the complexities in the field of neonatology on the issue of transfusions, there are a few studies that have related the risk factors of birthweight, gestational age and length of stay with transfusion status in these infants (Paul DA et al, 1997; Ringer et al, 1998). A study by Strauss reported that infants with birthweights less than 1500 grams received an average of 10 transfusions (Strauss, 1991). Brown and colleagues showed that gestational age less than 30 weeks to be most predictive of the need for two or

more transfusions (Brown et al, 1990). Other reports suggest that, among premature infants, those who are larger and with a longer gestation will require less transfusion support than smaller and more premature infants (Kilbride et al, 1988; Cook et al, 1993; Liu et al, 1994; Wang-Rodriguez et al, 1996). Paul and his associates were the first to correlate length of hospital stay with transfusion (Paul et al, 1997). Their findings showed that infants with a prolonged length of stay had increased phlebotomy losses and this caused an increase in the number of transfusions (Paul et al, 1997).

The purpose of the present study was to assess the relationship between neonatal mortality and birthweight, gestational age and transfusion, considering length of stay. The mortality analysis was extended to consider various types of blood products administered, unit exposures and donor exposures.

Methods

Data Collection and Study Population

Neonatal patient charts were extracted for the period of January 1978 to April 1992 for the University of Alberta Neonatal Intensive Care Unit (NICU). The years of 1982 and 1983 were not included in this study because the charts for these two years were either missing or destroyed. Alternative methods of identifying these patients were unsuccessful.

During this period, 7,993 infants were admitted to the NICU. The following information was abstracted from their charts:

1) birthweight in grams, gestational age in weeks, in-hospital mortality and transfusion status (Yes/No), per the discharge summary;
2) gender, death during follow-up and length of stay (days) from the admission sheet, subsequent admission sheet and/or medical records tandem checks;
3) blood components received, number of transfusions for each product and donor identification numbers from the chart transfusion sheets.

Information on death during follow-up was obtained on a regular basis from medical files, Provincial vital statistics and the Alberta Health Care Insurance Plan. Patients who were discharged alive from the NICU were followed until November 1998. Information pertaining to the date of death was collected from medical charts. However, the cause of death for the patient was not recorded. Completed information was available for 7,975 infants. Of the 18, 11 were missing gestational age; four were missing birthweights and three were missing for length of stay. There were 49 NICU re-admissions.

Statistical Analysis

Odds ratios, 95% confidence intervals and p-values were computed using standard contingency table methods for the relationship between mortality and birthweight, gestational age, gender, transfusion status and unit intervals for fresh frozen plasma (FFP), packed cells (PC) and a combination of all blood products (white blood cells [WBCs], cryoprecipitate, whole blood, platelets, FFP and PC) except albumin and IVIG.

For birthweight, 1501 to 2500 grams was used as the reference category. Although the birthweights of these babies would usually be considered low, their mortality rate was less than that of the larger babies. This suggests that babies with normal birthweights who are admitted to the NICU are more likely to have serious medical conditions other

than problems usually associated with prematurity. A similar rationale was used in defining 33 to 36 weeks as the reference category for gestational age. For unit exposure, non-transfused infants were the reference category.

Kaplan-Meier's product-limit method was used to calculate the length of in-hospital survival with the end-point of interest being mortality in the University of Alberta NICU for eight birthweight categories (0-500, 501-1000, 1001-1500, 1501-2000, 2001-2500, 2501-3500, 3501-4500 and ≥ 4501 grams) and six categories for gestational age (20-23, 24-28, 29-32, 33-36, 37-42 and ≥ 43 weeks). Patients were also stratified for transfusion status (transfused/non-transfused) and unit exposures for individual blood products such as FFP and PC as well as a group including "any the blood products except albumin and IVIG" (all were categorical as 1, 2-4, 5-10, 11-49 and ≥ 50 units).

Categorical and continuous variables were individually added to the Cox regression model containing discharge status (dead = 1, alive = 0) length of stay (continuous). Each variable was individually fitted in the model by determining its statistical significance at $\alpha = 0.05$. Those that were non-significant individually were not considered for the multivariate model. Stepwise forward and backward selection was performed starting with gestational age (continuous), which was highly statistically significant as judged by the Wald statistic and the change in the deviance. When birthweight (continuous) was added to the model the deviance of the model did not differ significantly from the model containing gestational age alone. With the addition of transfusion status (dichotomous), the model became unstable. Since birthweight and gestational age had the same odds ratios and beta coefficients, it was decided to keep gestational age in the model. When other variables were added to this model (e.g. unit

and donor exposures) the model became unstable. Thus the model showed gestational age and transfusion as the key risk factors for mortality.

Results

Approximately fifty percent of all neonates were in the normal range for birthweight (2501 to 4500 grams) and 46.6% of infants were in the normal range gestational age (37 to 42 weeks) (Table 5-1). There were more males (58%) than females (42%).

Sixteen percent of the infants were in the very low birthweight (VLBW) category (< 1500 grams) while 22.4% were pre-term infants. There were relatively fewer overweight and overdue babies: 1.3% and 0.6% respectively (Table 5-1). The mean ± SD for birthweight and gestational age was 2530 ± 959 grams and 36 ± 4 weeks respectively.

Overall, 46.2% of the neonates were transfused (Table 5-2). Most of the deaths occurred in the hospital (764 or 892). The overall mortality rate was 11.2% with 9.5% dying during the initial NICU admission. Overall survival of these infants was high at 88.8%. Thirty-six percent of infants stayed in the NICU between two to seven days. The mean ± SD for length of stay was 19 ± 32 days.

Table 5-1: Description of neonatal patients

Characteristics	n	%
Birthweight (grams)		
0 – 500	36	0.5
501 – 750	150	1.9
751 – 1000	299	3.7
1001 – 1500	819	10.3
1501 – 2500	2619	32.8
2501 – 4500	3964	49.6
≥ 4501	102	1.3
Total	7989	100
Gestational age (weeks)		
20 – 23	36	0.5
24 – 28	566	7.1
29 – 32	1185	14.8
33 – 36	2432	30.5
37 – 42	3718	46.6
≥ 43	45	0.6
Total	7982	100
Gender		
Male	4633	58.0
Female	3360	42.0
Total	7993	100

VLBW infants (0-500, 501-750, 751-1000 and 1001-1500 grams) had significantly elevated odds ratios (121.3, 29.4, 9.9 and 2.6, respectively). This was also true for

Table 5-2: Hospitalization characteristics of the neonatal patient population

Characteristics	n	%
Transfusion		
Transfused	3692	46.2
Non-transfused	4301	53.8
Total	7993	100
Overall mortality		
Died	892	11.2
Survived	7101	88.8
Total	7993	100
In-hospital mortality		
Died	764*	9.5
Survived	7229	90.5
Total	7993	100
Length of stay (days)		
< 1	261	3.2
1	410	5.1
2 - 7	2872	35.7
8 – 14	1680	20.9
15 – 30	1536	19.1
≥ 31	1280	15.9
Total	8039	100

* 8 of these deaths occurred during a second admission to the NICU

pre-term infants (20-23, 24-28 and 29-32 weeks) with odds ratios of 280.0, 11.8 and 1.7 respectively (Table 5-3).

Table 5-3: Comparison of those who died during follow-up with those who survived for selected risk factors

Characteristics	Died		Survived		Odds ratio	95% confidence interval	p-value
	n	%	n	%			
Birthweight (grams)							
0 – 500	32	88.9	4	11.1	121.3	42.4, 347.1	< 0.0001
501 – 750	99	66.0	51	34.0	29.4	20.3, 42.7	< 0.0001
751 -1000	118	39.5	181	60.5	9.9	7.5, 13.1	< 0.0001
1001 - 1500	119	14.5	700	85.5	2.6	2.0, 3.3	< 0.0001
1501 - 2500	162	6.2	2457	93.8	1.0	Reference category	
2501 - 4500	356	9.0	3608	91.0	1.5	1.2, 1.8	< 0.0001
≥ 4501	5	4.9	97	95.1	0.8	0.3, 1.9	0.60
Gestational age (weeks)							
20 – 23	34	94.4	2	5.6	280.0	66.6, 1176.8	< 0.0001
24 – 28	236	41.7	330	58.3	11.8	9.3, 15.0	< 0.0001
29 – 32	113	9.5	1072	90.5	1.7	1.3, 2.3	< 0.0001
33 – 36	139	5.7	2293	94.3	1.0	Reference category	
37 – 42	362	9.7	3356	90.3	1.8	1.5, 2.2	< 0.0001
≥ 43	5	11.1	40	88.9	2.1	0.8, 5.3	0.13
Gender							
Female	409	12.2	2951	87.8	1.2	1.0, 1.4	0.014
Male	483	10.4	4150	89.6	1.0	Reference category	
Transfusion							
Transfused	673	18.2	3019	81.8	4.2	3.5, 4.9	< 0.0001
Non-transfused	219	5.1	4082	94.9	1.0	Reference category	

Mortality for infants who would usually be considered normal for birthweight (2501-4500) and gestational age (37-42 weeks) were at significantly higher risk for mortality compared to the reference categories (OR = 1.5, 95% CI: 1.2, 1.8 and OR = 1.8, 95% CI: 1.5, 2.2 respectively).

Transfused patients had a four-fold increase in mortality compared to those who were not transfused. Length of stay in the NICU of less than one day or less was associated with a high risk of mortality. Compared to the reference category of two to seven days, those with a length of stay from eight to 30 days had lower mortality and those staying longer than 30 days had higher mortality.

For the category "any blood products except albumin and IVIG" and the individual blood products all of the odds ratios for mortality in terms of unit exposures were significantly different from the reference category of non-transfused infants (Table 5-4). In general, mortality increased with increasing unit exposures for each category. The odds ratio for 50 or more units of packed cells was not calculated due to small numbers.

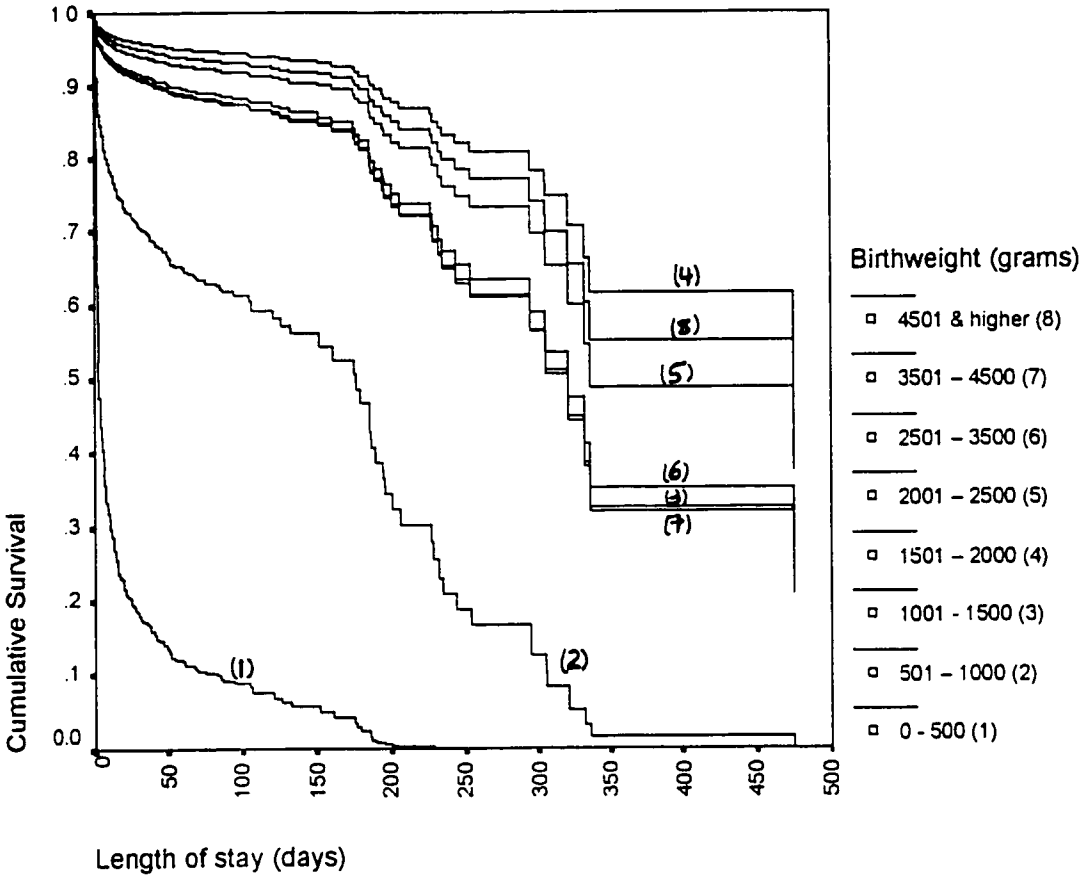
Cumulative survival for VLBW infants was worse than the normal birthweight infants (Figure 5-1). The highest survival was observed for those with birthweights of 1501 to 2000 grams, more than 4500 grams and 2001 to 2500 grams. Survival for those with birthweights of 1000 to 1501 grams and 3501 to 4500 grams was nearly identical.

None of the survival curves for the gestational age categories overlapped (Figure 5-2). The worst survival was seen for infants born less than 29 weeks gestation and best for those between 29 and 36 weeks.

Table 5-4: Comparison of those who died during follow-up with those who survived for selected blood products

Unit exposures for selected blood products	Died		Survived		Odds ratio	95% confidence interval	p – value
	n	%	n	%			
Non-transfused	219	2.7	4082	51.1	1.0	Reference category	
Fresh Frozen Plasma (FFP)							
1	147	33.0	601	42.4	4.6	3.6, 5.7	< 0.0001
2 – 4	173	38.9	477	33.7	6.8	5.4, 8.4	< 0.0001
5 – 10	75	16.9	252	17.8	5.5	4.1, 7.4	< 0.0001
11 – 49	47	10.6	85	6.0	10.3	7.0, 15.1	< 0.0001
50 and higher	3	0.7	1	0.1	55.9	5.8, 539.6	0.0005
Total	445	100	1416	100			
Packed Cells (PC)							
1	165	27.8	837	36.8	3.7	3.0, 4.6	< 0.0001
2 – 4	219	36.9	940	41.3	4.4	3.6, 5.3	< 0.0001
5 – 10	123	20.7	350	15.4	6.6	5.1, 8.4	< 0.0001
11 – 49	85	14.3	148	6.5	10.7	8.0, 14.5	< 0.0001
50 and higher	1	0.2	0	-		Not calculated	
Total	593	100	2275	100			
Any blood products except albumin and IVIG							
1	115	17.9	817	30.8	2.6	2.1, 3.3	< 0.0001
2 – 4	205	31.8	985	37.1	3.9	3.2, 4.8	< 0.0001
5 – 10	150	23.3	505	19.0	5.6	4.4, 7.0	< 0.0001
11 – 49	163	25.3	335	12.6	9.1	7.2, 11.5	< 0.0001
50 and higher	11	1.7	11	0.4	18.7	8.0, 43.6	< 0.0001
Total	644	19.5	2653	81.5			

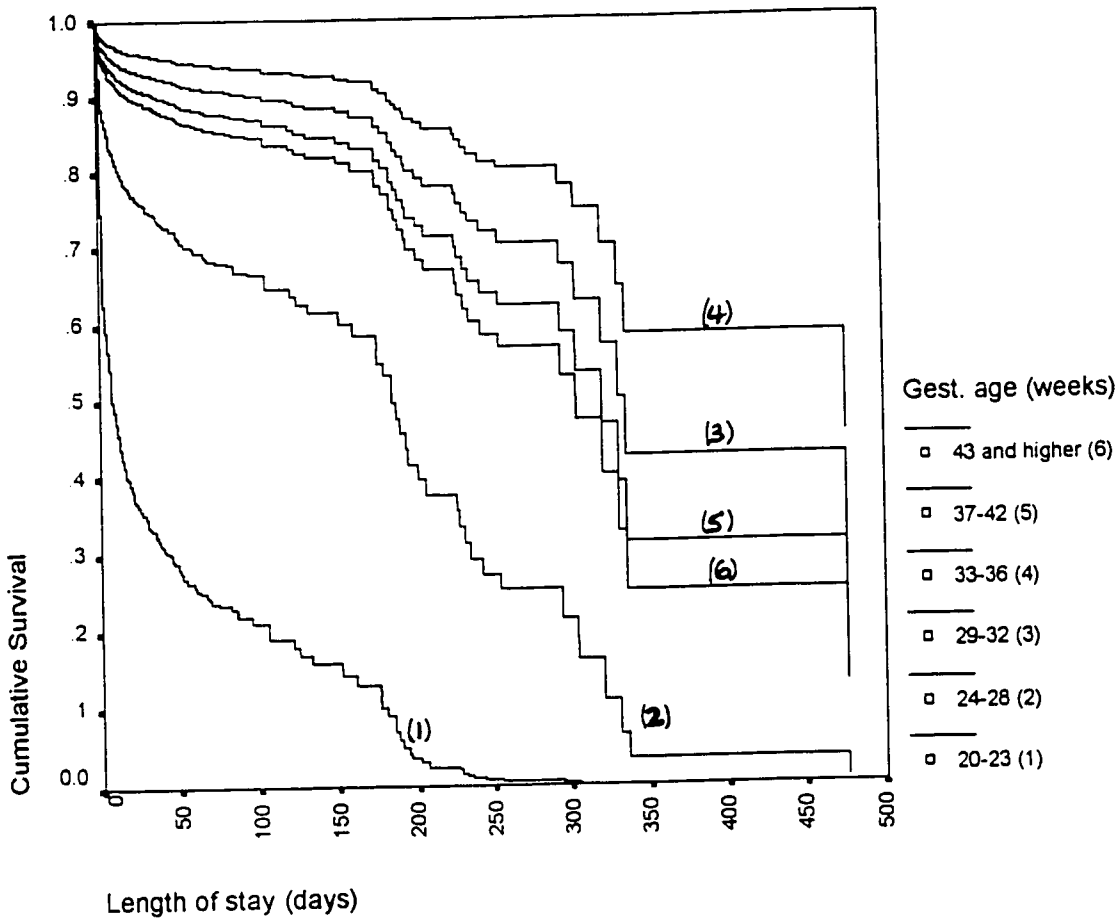
Figure 5-1: Cumulative probability survival for neonates in the eight-birthweight intervals



Infants who were transfused had lower cumulative survival compared to those who were not transfused (Figure 5-3).

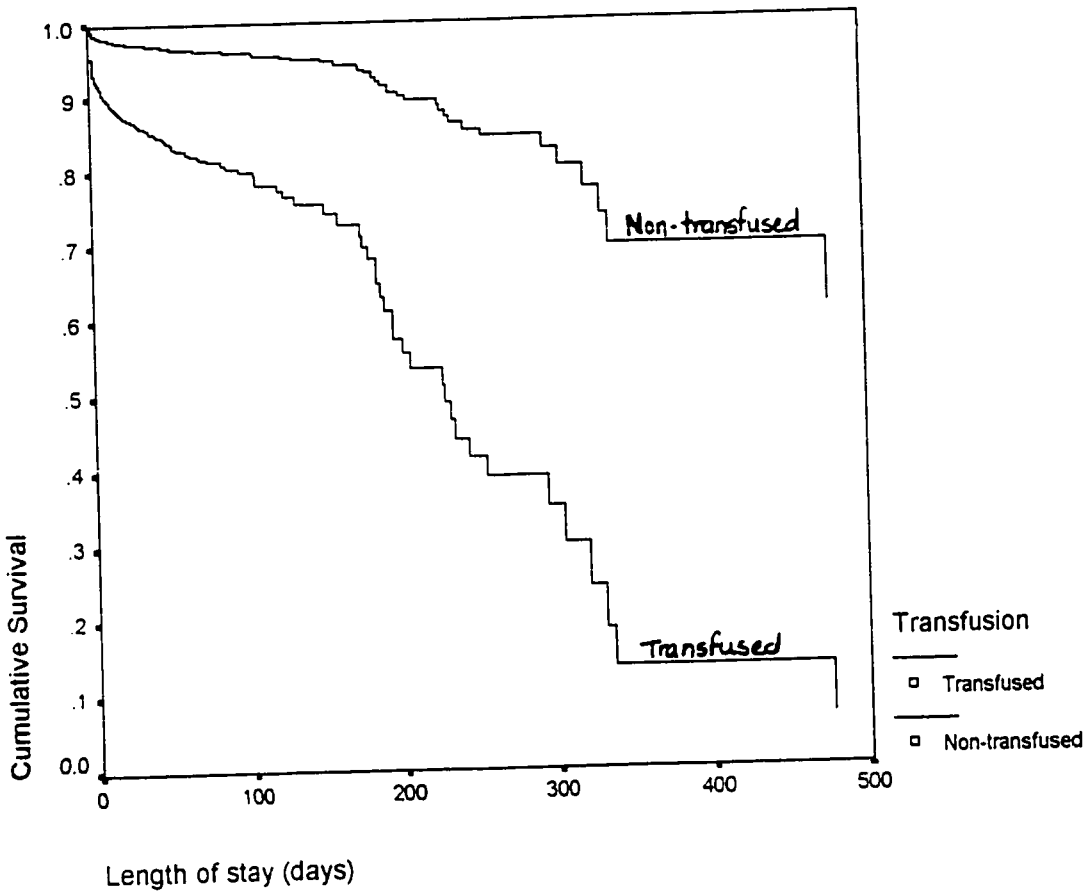
In Figure 5-4, the survival curves for categories of unit exposure to FFP overlapped extensively. The survival curves were similar for infants who received either one unit or five to ten units of FFP and overlap was also seen for those receiving two to four and 11 to 49 units. Survival was worst for infants who received 50 or more units of FFP, and best for those receiving either one unit or five to ten units.

Figure 5-2: Cumulative survival probability for neonates in the six gestational age intervals



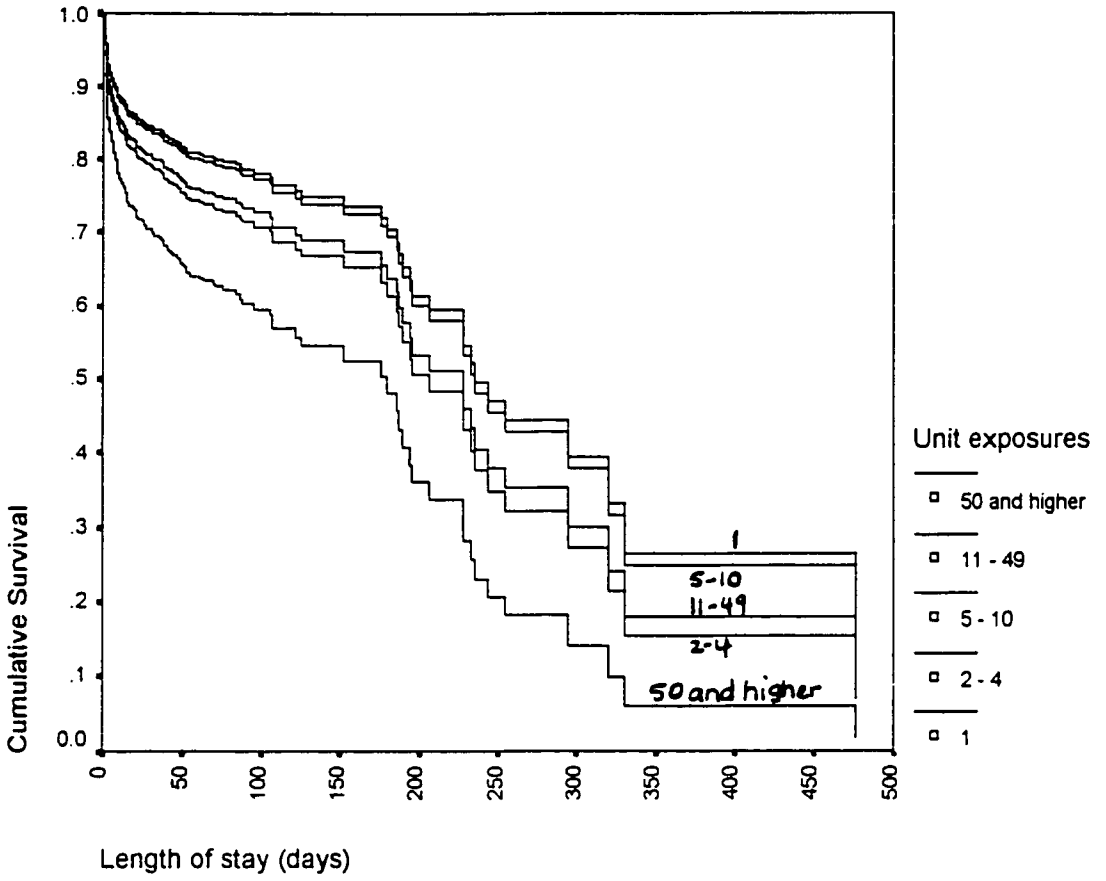
For packed cells there was very little difference in survival through the range from two to 49 units (Figure 5-5). Again, survival for infants given 50 or more units was the worst and was comparable to the findings for FFP. However, best survival was seen in the infants who received only one unit of PC.

Figure 5-3: Cumulative probability survival for neonates that are transfused and non-transfused



The pattern was somewhat different when the category for "any blood product except albumin and IVIG" was considered (Figure 5-6). There was no overlap between the unit exposure categories. The best survival was seen for neonates who were given only one unit of any of the six products (viz., WBC, cryoprecipitate, whole blood, platelets, FFP and PC). On the other hand, the worst survival was found in the group of infants who received a combination of these products with unit exposures varying from 11 to 49. Infants who received 50 or more units had better survival than those who received two to four units or five to ten units.

Figure 5-4: Cumulative probability survival for neonates who receive fresh frozen plasma (FFP) units



The Cox regression analysis revealed a significant association between survival and both gestational age (weeks) and transfusion status (Table 5-5). The odds ratio for an infant being transfused was 5.02 suggesting risk of mortality associated with a transfusion while the odds ratio for gestational age was significantly less than one indicting that lower gestational age was associated with increased risk of mortality. The likelihood ratio statistic (233.455, $p < 0.0001$) indicated that the null hypothesis was rejected and that the model was useful for predicting in-hospital mortality.

Figure 5-5: Cumulative probability survival for neonates who receive packed cell (PC) units

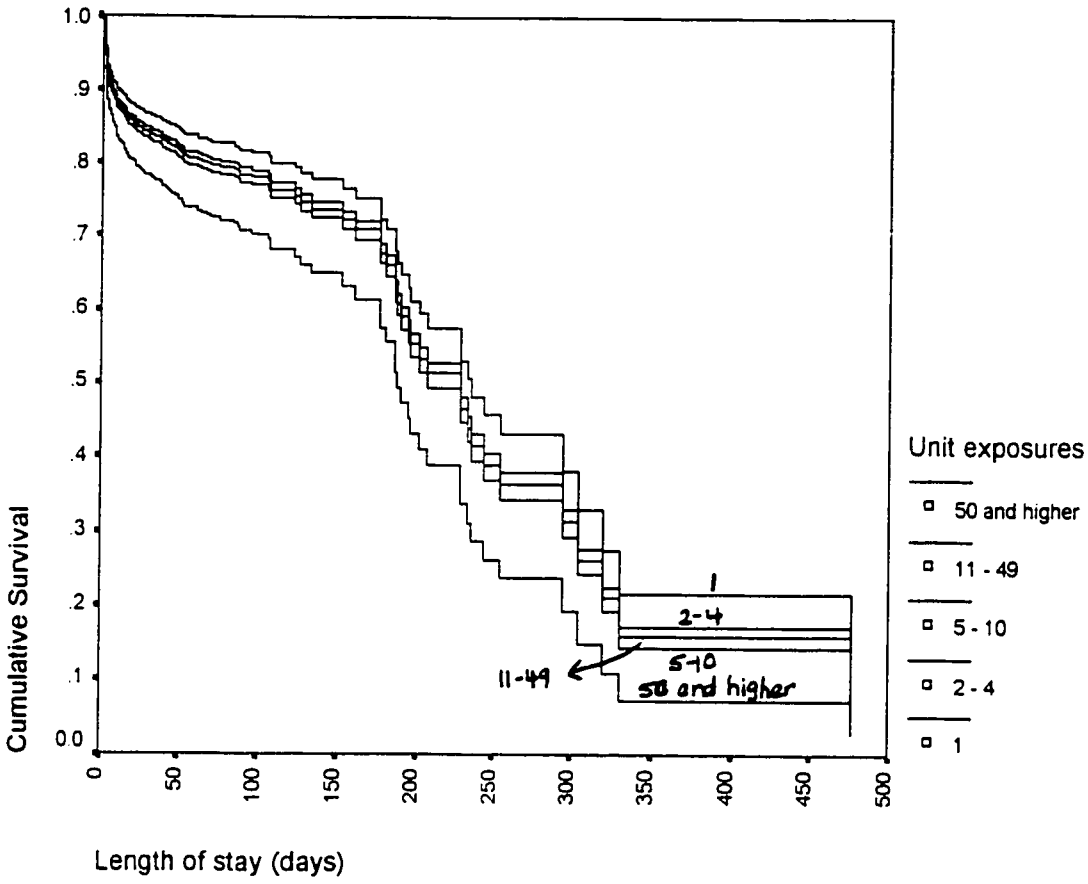


Figure 5-6: Cumulative probability survival for neonates who receive "any blood products except albumin and IVIG" units

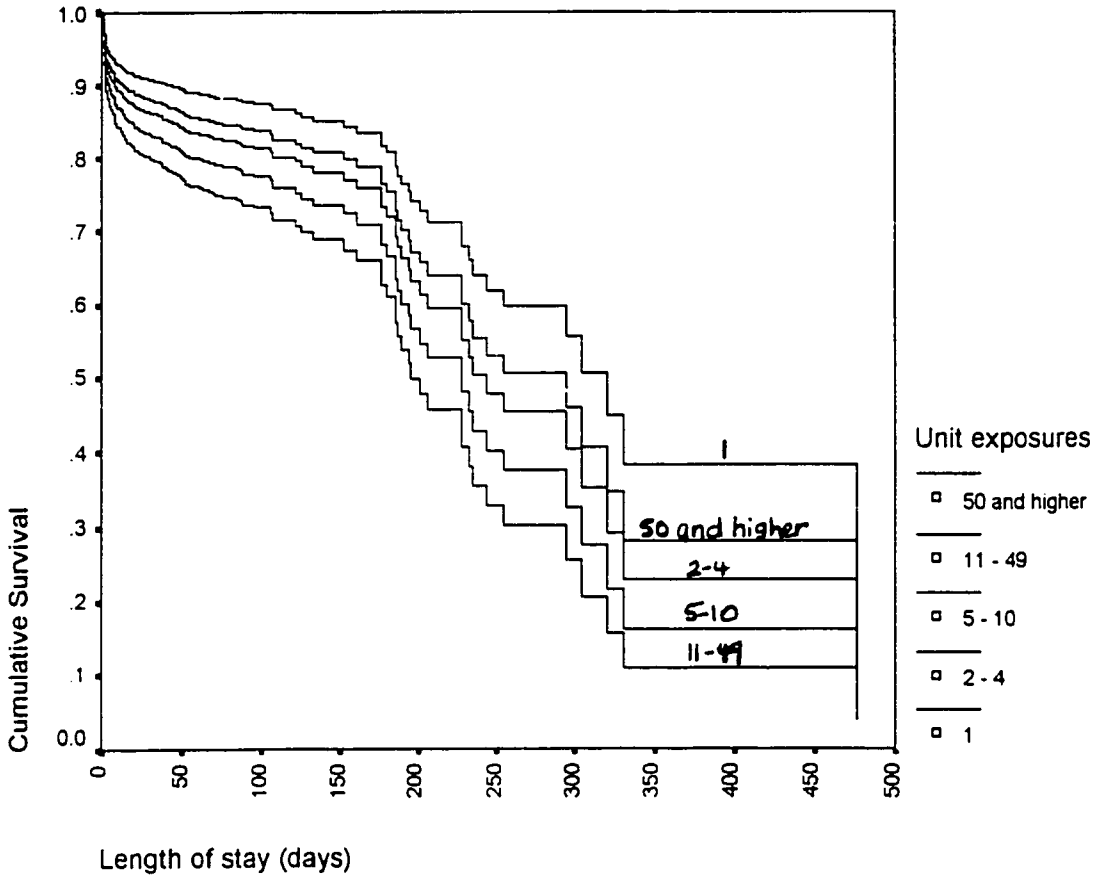


Table 5-5: Multivariate Cox regression model for discharge status (deceased = 1, alive = 0) and length of stay (continuous)

Variables	Estimated coefficient (B)	Odds ratio (Exp B)	95% confidence interval	p-value
Baseline Model				
Gestational age (weeks)	-0.0340	0.97	0.95, 0.99	0.0004
Transfused (1 = Yes, 0 = No)	1.6138	5.02	3.88, 6.51	0.0000

Deviance = 8816.072

Likelihood Ratio Statistic = 233.455, df = 2

P < 0.0001

Discussion

Almost half of the infants that were admitted to the NICU fell in the category of normal birthweight and gestational age. These infants probably had other significant underlying diseases that required admittance to the NICU, otherwise they would have been transferred to the nursery. There were fewer infants classified as VLBW or pre-term. Thus the population that entered the NICU was not just small and premature but also included larger and more mature infants. Although few studies exist in this area, most

are concerned exclusively with VLBW or pre-term infants. Most of the infants had a length of stay in the NICU two to seven days. However, a small percentage (8.3%) of infants stayed for one day or less. The percentage of infants who stayed at least 15 days was 35%. These were the neonates who received most of the transfusion support.

A strong and statistically significant elevation in for mortality was found for infants who weighed less than 1500 grams, were younger than 29 weeks, who were transfused and who stayed in the NICU for one day or less. The Malaysian Very Low Birth Weight Study Group found similar results except that receipt of a transfusion was associated with a lower risk of mortality in their study (Malaysian Very Low Birth Weight Study Group, 1997). However, the Malaysian study looked at VLBW and pre-term infants whose blood transfusions may increase their chances of survival as they replace phlebotomy losses due to laboratory tests and improve erythropoiesis functions (Ringer et al, 1998; Bruce and Roe, 1997). The difference in the results may be related to the fact that the present study included all NICU patients regardless of weight or gestational age. The decision to receive a transfusion in this population may be influenced by the prematurity of the infant, in addition, to the size and underlying diseases that require transfusion support. These conditions may include intraventricular or intracranial hemorrhages, necrotizing enterocolitis and congenital heart disease. Further analysis incorporating discharge diagnoses (not available for the present study) may further clarify this relationship. The high mortality among patients with a length of stay of less than or equal to one day was probably due to the rapid demise of infants who are critically ill and/or premature.

Most studies that have evaluated individual blood products have tried to determine unit and donor exposures as well as factors that may contribute to better transfusion

practices. The relationship between the use of different blood products to mortality has not been reported previously in the neonatal population. For all of the individual blood products and groups of products, a statistically significant and positive association was seen with mortality. While a role of transfusion per se as risk factor for mortality is possible, this is not possible to assess without detailed information on the nature and severity of the underlying conditions (not possible in this study).

Analysis of the survival curves corroborated the findings of the bivariate analysis. Survival was worst in infants who weighed less than 1500 grams, were younger than 28 weeks and were transfused. The survival curves for birthweight tended to overlap suggesting that as a categorical variable, birthweight was not as predictive of survival as gestational age. The survival curves for categories of gestational age were more clearly separated. The highest survival was in the group that weighed between 1501 and 2000 grams. For the normal birthweight ranges of 2501 to 3500 and 3501 to 4500 grams, survival was lower than for the group weighing 2001 to 2500 grams, probably because normal birthweight infants would only enter the NICU if they had other significant complications. For gestational age, survival was best for the group of infants between 33 and 36 weeks. Again, normal term infants had lower survival suggesting other conditions or complications in this group. Distinct survival curves were observed for transfusion status with those receiving a transfusion at a significant disadvantage for survival.

The types of blood products administered and the number of units received by neonates were also related to survival but in a different manner. FFP and PC were analyzed separately because the first product is used to treat coagulation factor deficiencies and bleeding (Blanchette et al, 1991) while PC is used to replace acute blood losses and to

restore hemoglobin and hematocrit levels caused either by anemia or prematurity (Simon et al, 1998). For the survival curves of these products, there was considerable overlap between the unit exposure intervals. However, worst survival was seen for both products in the infants that received more than or equal to 50 units. A study by Oblanden and his colleagues found a strong correlation between the volume of blood drawn and the volume of blood transfused (Obladen et al, 1988). This was also seen in a study conducted by Shannon and associates (Shannon et al, 1991). Since the amount of blood in a transfused to neonates is directly related to phlebotomy losses, noninvasive monitoring techniques and laboratory micro-methods for withdrawing blood may greatly reduce the need for transfusions.

The survival analysis depicted a different picture for "any blood products except albumin and IVIG". Here, survival was better for infants who received 50 or more units. Infants who receive 50 or more units of the combined blood products usually stay in the hospital for a prolonged period of time. As their length of stay increases, so does their maturity, organ and immune system function and size. All of this may explain the improved survival seen for receipt of 50 or more units of "any blood products except for albumin and IVIG". Nevertheless, a neonate receiving only one unit of any blood product still had a better survival outcome in the end, suggesting a less serious underlying condition. Worst survival was observed for babies receiving these blood products in a range of units varying from 11 to 49.

The results found here are different than the result of the study performed by Vamvakas and Taswell (Vamvakas and Taswell, 1994). They found that shorter survival after a blood transfusion was correlated with male *gender*, greater age, receipt of blood components for the treatment of a medical disease as opposed to surgery, receipt of

platelets, fresh frozen plasma (FFP) or more than 10 units of red blood cells (RBCs) in adults. One similarity is that in both studies use of FFP and PC was related to mortality. However, the unit exposures differed significantly. The demographics of their population cannot be applied here in its entirety. The difference in the findings of the two studies highlights the importance of treating neonates differently from older children and adults.

A Cox regression model showed that the continuous independent variables of gestational age and transfusion were significantly related to survival. Introduction of birthweight into the model caused instability. The correlation coefficient for birthweight and gestational age was found to be 0.85. Because birthweight can be high even in premature infants (for instance, a baby of a diabetic mother). It was decided to introduce gestational age alone in the model.

The objective of this paper was to establish the relationship between mortality and survival time and certain risk factors such as birthweight, gestational age, transfusion status, types of blood products and unit exposures of these blood products. The results showed that these risk factors have a considerable effect on mortality and survival time. However, the clinical outcome is worse for infants who are in the category of VLBW, pre-term and transfused with blood products such as packed cells and fresh frozen plasma. These observations may lead to a better understanding of transfusion practices and the basic physiology in neonates.

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Chapter 6

Changes in Transfusion Practices and an Estimation of the Incidence of Hepatitis C Virus (HCV) Infection in Transfused Neonates at the University of Alberta Neonatal Intensive Care Unit for the Years of January 1978 to April 1992

Introduction

Although transfusion of blood products is an essential and potentially life-saving measure, not all blood transfusions are beneficial to patients (Heddle et al, 1997; Blanchette et al, 1991). This is especially true for neonates who undergo an estimated 300,000 transfusions in the United States annually (Strauss, 1991). Transfusions of blood components are indispensable to the modern care of the critically ill, especially premature infants (Strauss, 1991). However, blood transfusion is not without risk and the potential for adverse outcomes is even greater in those very tiny patients who often have immature organ function and/or are critically ill (Hume and Blanchette, 1995). Most infants who undergo transfusion are exposed to multiple blood donors, and although each exposure poses only a small risk, the potential for adverse effects of multiple transfusions and donor exposures is not trivial (Strauss, 1991). The increased risk of transmission of infectious disease and the potential for transmission to multiply transfused infants of as yet unidentified infectious agents are major concerns in neonatal transfusion practice (Wang-Rodriguez et al, 1996).

The use of empirically derived transfusion guidelines has been demonstrated to safely reduce the number of transfusions and different donors to whom premature infants are exposed (Bifano et al, 1995). However, the changes in transfusion practices over the years before these transfusion guidelines were implemented have not been thoroughly evaluated (Widness et al, 1996). They studied the changes in the pattern of RBC transfusions given to VLBW infants admitted to the nursery at the University of Iowa Hospital and Clinics for a twelve-year period. There was a significant decrease in the percentage of infants who received transfusions of RBCs ($p = 0.006$) and the number of RBC given to each infant ($p < 00001$) (Widness et al, 1996). This decrease was

primarily associated with an increase in the percentage of relatively large pre-term infants (birthweight 1.0 – 1.5 kg) who did not require any RBC transfusions: 17% in 1982, 33% in 1989 and 64% in 1993 ($p = 0.0006$) (Widness et al, 1996).

The safety of the blood supply continues to increase, not only as a result of major innovations such as the elimination of donations not given voluntarily and the introduction of new screening tests, but also because of incremental improvements in test sensitivity and refinements in the process of educating donors and assessing their qualifications (Dodd, 1992). Only a small proportion of infections with other transfusion-transmitted agents result in clinically recognized disease, and in most cases the disease occurs many years after the transfusion (Dodd, 1992). This is true in the transmission of Hepatitis C Virus (HCV) in neonates.

The purpose of the present study was to describe the changes in transfusion practices in the University of Alberta Neonatal Intensive Care Unit (NICU) during the period from January 1978 to April 1992 (not including 1982 and 1983). These years were chosen to capture important milestones in the development of Canada's blood supply. From November 1985 Canada's donor blood supply underwent screening for antibodies to HIV and in 1990 screening for HCV antibodies began. Transfusion data, including unit and donor exposures, were also used to estimate the number of children likely to have been infected with HCV and the number of those infants surviving through 1998.

Methods

Data Collection and Study Population

Neonatal patient charts were extracted for the period January 1978 to April 1992. The years of 1982 and 1983 were not included in this study because the charts for these two years were either missing or destroyed. Alternative methods of identifying these patients were unsuccessful.

During this period, 7,993 infants were admitted to the NICU. The following information was abstracted from their charts:

1) birthweight in grams, gestational age in weeks, in-hospital mortality (Yes/No) and transfusion status (Yes/No), per the discharge summary;
2) gender, death during follow-up and length of stay (days) from the admission sheet, subsequent admission sheet and/or medical records tandem checks;
3) blood components received, number of transfusions for each product and donor identification numbers from in the chart transfusion sheets.

Information on death during follow-up was obtained on a regular basis from medical files, Provincial vital statistics and the Alberta Health Care Insurance Plan. Patients who were discharged alive from the NICU were followed until November 1998. Information pertaining to the date of death was collected from medical charts. However, the cause of death for the patient was not recorded. Unit exposures refer to the number of units received while donor exposures are the number of different donors the recipient is exposed to while being transfused.

Completed information was available for 7,975 infants. Of the 18, 11 were missing gestational age; four were missing birthweights and three were missing length of stay. There were 49 NICU re-admissions.

Statistical Analyses

All statistical analyses were performed with standard statistical software (SPSS). Demographics and hospitalization characteristics were derived using frequency distributions and cross-tabs during the period from January 1978 to April 1992. These analyses were repeated for each year from 1978 to 1992 and by year for infants who weighed less than or equal to 1500 grams and those who weighed more than 1500 grams. Bar charts were use to describe the trend for the percentage of infants who were transfused during this time period. The percentage of units used during this time period was determined by dividing the number of units for individual blood products such as whole blood, platelets, fresh frozen plasma (FFP) and packed cells (PC) and albumin over the total number of units of all blood products except IVIG. These percentages were then plotted in a line chart.

To evaluate the trend in unit exposures and donor exposures for FFP and PC and the category including "any blood products except albumin and IVIG", donor exposures for each individual infant was divided by its correlated unit exposure. The mean and the standard deviation of this value for all the infants were then plotted for each year.

Prevalence of hepatitis C in the general population was obtained from the report of the expert panel on hepatitis C (unpublished) conducted by Health Canada in 1998 (Remis, 1998). The unit exposure risk for HCV in the neonatal population was calculated by multiplying the prevalence of each year with the numeric unit exposures of each individual infant who was transfused. A sum of all the individual unit exposures was computed for each year and mean ± standard deviations of unit exposure risk were calculated. The number of infants likely to be infected with hepatitis C was obtained by

multiplying the mean unit exposure risk in a particular year by the number of infants transfused with "any of the blood products except albumin and IVIG". In addition, survival estimates for the infants were obtained from the Kaplan-Meier survival curves for each year and number of infected infants surviving was calculated by multiplying the survival estimates with the number of infants who were transfused with "any of the blood products except albumin and IVIG". Ranges were computed for the number of infants that are likely to have been infected with HCV and the number of surviving infants infected likely to have been infected with HCV using standard deviations for each of the estimates.

Results

The number of admissions remained fairly constant during the time period from January 1978 to April 1992 at the University of Alberta NICU (Table 6-1). The percentage of infants transfused decreased after 1985. However, there was an increase observed after 1988, although the percent transfused remained lower than for the pre-1986 period. None of the other variables showed a noticeable trend during this time period.

With the exception of 1978, 1979 and 1988, the percentage of infants weighing less than or equal to 1500 grams remained fairly constant. Infants (less than or equal to 1500 grams) were transfused more often and stayed longer in the NICU compared to the larger infants. However, overall and in-hospital mortality was generally higher in the larger infants compared to the smaller infants. No particular trend was observed in the relative survival of the two groups during this time period.

Table 6-1: Description of demographic and hospitalization characteristics from January 1978 to April 1992

Characteristics	Years												
	1978	1979	1980	1981	1984	1985	1986	1987	1988	1989	1990	1991	1992
Neonates (n)	459	642	679	664	701	629	676	673	732	712	619	577	230
Birthweight (grams, Mean ± SD)*	2612 ± 924	2590 ± 911	2463 ± 929	2457 ± 928	2541 ± 1015	2571 ± 974	2552 ± 950	2519 ± 933	2598 ± 956	2480 ± 976	2521 ± 989	2487 ± 996	2494 ± 976
Gestational age (weeks, Mean ± SD)^	36 ± 4	36 ± 4	36 ± 4	36 ± 4	36 ± 4	36 ± 4	36 ± 4	36 ± 4	36 ± 4	35 ± 4	36 ± 4	35 ± 5	35 ± 5
Transfused (n, %)^	222 (48.4)	337 (52.5)	339 (49.9)	338 (50.9)	360 (51.4)	342 (54.4)	284 (42.0)	239 (35.5)	262 (35.8)	334 (46.9)	269 (43.5)	268 (46.4)	98 (42.6)
Overall mortality (n, %)*	51 (11.1)	72 (11.2)	96 (14.1)	79 (11.9)	91 (13.0)	78 (12.4)	88 (13.0)	70 (10.4)	63 (8.6)	75 (10.5)	57 (9.2)	49 (8.5)	23 (10.0)
In-hospital mortality (n, %)#	46 (10.0)	60 (9.3)	88 (12.8)	73 (10.9)	78 (11.0)	68 (10.7)	72 (10.6)	58 (8.5)	53 (7.2)	65 (9.1)	41 (6.6)	41 (7.1)	21 (9.1)
Length of Stay (days, Mean ± SD)*	15.4 ± 24.6	16.7 ± 19.2	16.0 ± 23.9	17.8 ± 26.4	18.8 ± 26.4	19.0 ± 26.9	18.4 ± 23.7	20.4 ± 32.4	17.8 ± 27.1	18.4 ± 28.6	21.6 ± 67.1	21.2 ± 40.2	17.2 ± 24.9

SD = Standard Deviation
* $p < 0.05$
^ $p < 0.001$
# $p < 0.005$

Table 6-2: Description of demographic and hospitalization characteristics for neonates weighing less or greater than 1500 grams from January 1978 to April 1992

Characteristics	Years												
	1978	1979	1980	1981	1984	1985	1986	1987	1988	1989	1990	1991	1992
Neonates (n, %)$													
≤ 1500 grams	53	88	123	112	118	101	107	111	101	132	108	112	38
	(11.5)	(13.7)	(18.1)	(16.9)	(16.8)	(16.1)	(15.9)	(16.5)	(13.8)	(18.5)	(17.5)	(19.4)	(16.5)
> 1500 grams	406	553	556	552	583	528	568	562	631	580	509	465	192
	(88.5)	(86.3)	(81.9)	(83.1)	(83.2)	(83.9)	(84.1)	(83.5)	(86.2)	(81.5)	(82.5)	(80.6)	(83.5)
Transfused (n, %)													
≤ 1500 grams#	44	77	91	99	94	89	84	74	73	103	82	87	29
	(83.0)	(87.5)	(74.0)	(88.4)	(79.7)	(88.1)	(78.5)	(66.7)	(72.3)	(78.0)	(75.9)	(77.7)	(76.3)
> 1500 grams^	178	259	248	239	266	253	200	165	189	231	186	181	69
	(43.8)	(46.8)	(44.6)	(43.3)	(45.6)	(47.9)	(35.2)	(29.4)	(30.0)	(39.8)	(36.5)	(38.9)	(35.9)
Overall mortality (n, %)													
≤ 1500 grams#	20	26	47	33	43	31	32	30	19	32	19	23	13
	(4.4)	(4.0)	(6.9)	(5.0)	(6.1)	(4.9)	(4.7)	(4.5)	(2.6)	(4.5)	(3.1)	(4.0)	(5.7)
> 1500 grams*	31	46	49	46	48	47	56	40	44	43	37	26	10
	(6.8)	(7.2)	(7.2)	(6.9)	(6.8)	(7.5)	(8.3)	(5.9)	(6.0)	(6.0)	(6.0)	(4.5)	(4.3)
In-hospital mortality (n, %)													
≤ 1500 grams#	20	24	46	32	41	30	31	28	19	31	17	21	13
	(4.4)	(3.7)	(6.8)	(4.8)	(5.8)	(4.8)	(4.6)	(4.2)	(2.6)	(4.4)	(2.7)	(3.6)	(5.7)
> 1500 grams*	26	36	42	41	36	37	41	29	34	34	24	20	8
	(5.7)	(5.6)	(6.2)	(6.2)	(5.1)	(5.9)	(6.1)	(4.3)	(4.6)	(4.8)	(3.9)	(3.5)	(3.5)
Length of stay (days, Mean ± SD)$													
≤ 1500 grams	32.2 ± 34.4	39.0 ± 31.8	33.1 ± 39.2	42.0 ± 40.2	45.4 ± 45.5	50.0 ± 45.1	42.8 ± 41.9	45.5 ± 46.2	53.9 ± 48.9	45.4 ± 38.7	63.3 ± 149.3	58.6 ± 61.3	48.3 ± 45.0
> 1500 grams	13.2 ± 22.2	13.2 ± 13.3	12.0 ± 16.9	12.7 ± 19.0	13.4 ± 15.9	13.2 ± 16.3	13.8 ± 14.3	15.2 ± 26.1	12.0 ± 15.1	12.2 ± 21.6	12.9 ± 18.8	12.3 ± 26.3	11.0 ± 10.9

SD = Standard Deviation

* p is non-significant, ^ $p < 0.001$, # $p \leq 0.005$, $ $p < 0.05$

Figure 6-1: Percentage of neonates transfused with any blood products except albumin and IVIG

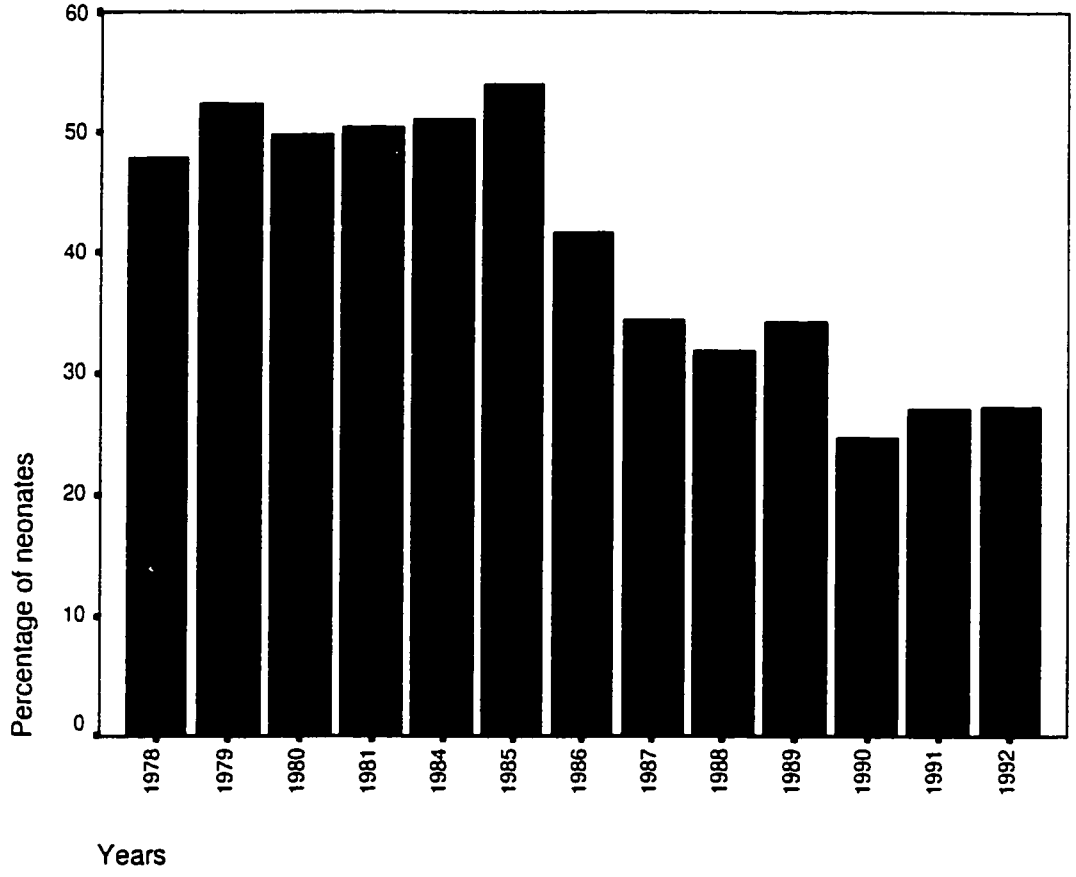


Figure 6-1 shows that the percentage of neonates being transfused with various blood products excluding albumin and IVIG decreased over the years. A sharp decline occurred after 1985 where the percentage dropped approximately 15%. Another drop was observed between 1985 and 1989 where the percentage fell approximately 19%. Overall the decrease in the number of infants transfused with blood products other than albumin and IVIG decreased almost 30%.

Figure 6-2: Percentage of blood product usage from January 1978 to April 1992 for packed cells, fresh frozen plasma, whole blood, platelets and albumin

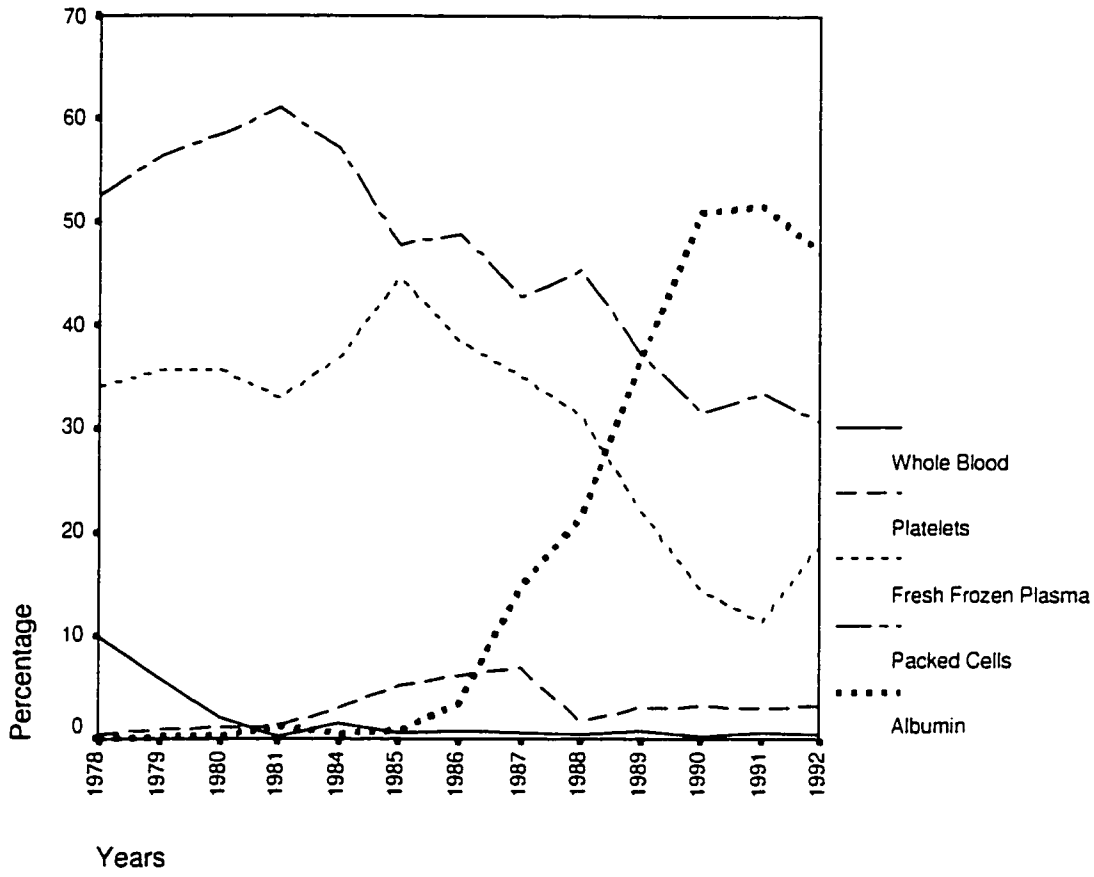
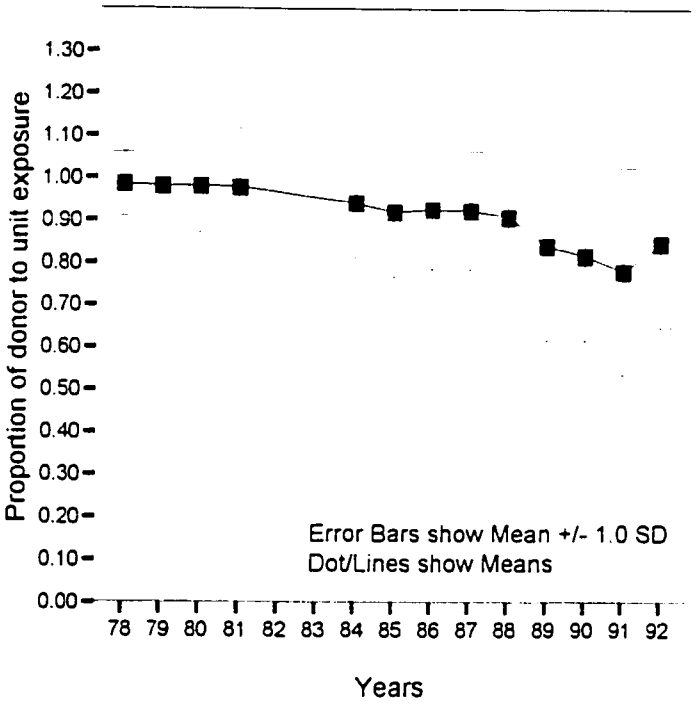


Figure 6-2 shows the changes in the use of individual blood products over time. Decreases were noticed for fresh frozen plasma and packed cells. For packed cells, the decrease began in 1981 and continued steadily until 1990 where a plateau was reached. The use of packed cells went from its maximum of 60% of all blood products used except IVIG for each year to almost 30%.

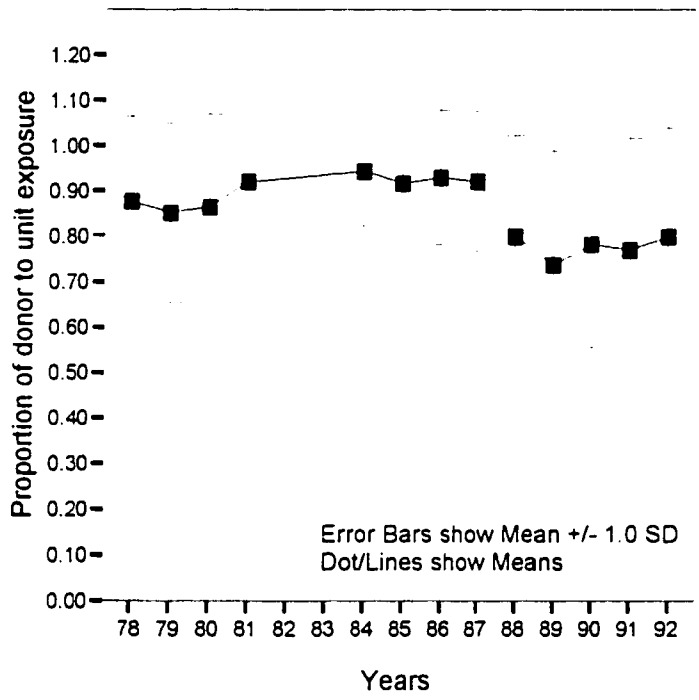
Figure 6-3: Mean ± standard deviation for the proportion of donor to unit exposures for fresh frozen plasma



The peak for fresh frozen plasma was in 1985. From 1985, use decreased significantly with a slight increase in 1992. Fresh frozen plasma use decreased from a maximum of 45% of all blood products except IVIG to a minimum of 10%.

Albumin usage increased significantly after 1986 and peaked in 1990. Its use increased from a minimum of almost 0% of all blood products except IVIG to a maximum of approximately 52%.

Figure 6-4: Mean ± standard deviation for the proportion of donor to unit exposure for packed cells



For the remaining two products, the changes were slight (Figure 6-2). Whole blood usage went from 10% in 1978 to almost zero after 1980. Platelet usage remained almost constant with slight increases observed in the years of 1984 to 1987.

Figure 6-3 depicts the proportion of the mean donor to unit exposure for FFP. From 1978 to 1988, neonates who were transfused with FFP were exposed to almost the same number of donors as units. The decline in donor to unit exposures after 1988 suggests a change in practice to decrease donor exposures.

Figure 6-5: Mean ± standard deviation for the proportion of donor to unit exposure for any blood products excluding albumin and IVIG

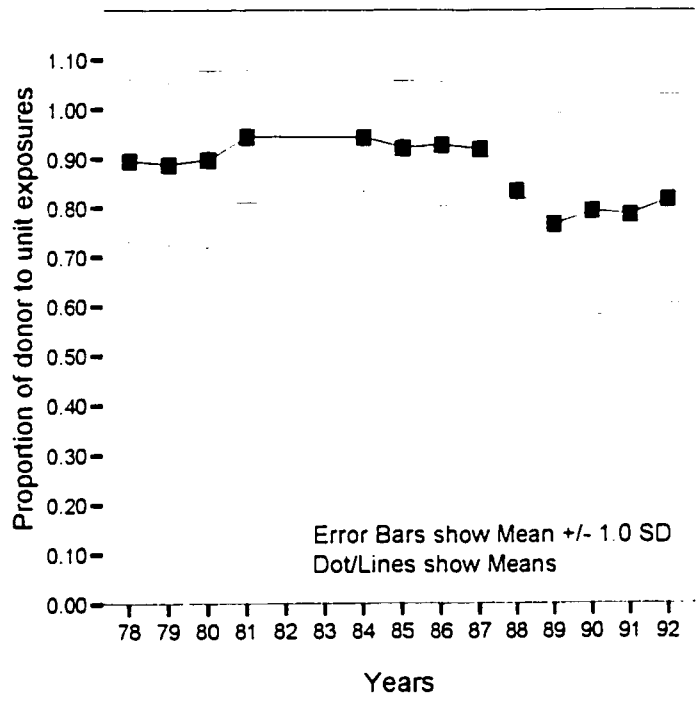


Figure 6-4 shows that mean donor to unit exposure for packed cells decreased after 1987. However, the ratios were lower than the ratios for FFP and for the years prior to 1987 donor to unit exposures were at about or above 0.9. After 1987, the decrease was dramatic and as low as 0.5.

The same conclusions can be drawn for the mean donor to unit exposure for "any blood products except for albumin and IVIG" in neonates as shown in Figure 6-5. Again, a marked change occurred after 1987 and the decrease in donor exposure followed the same trend as that of packed cells. The largest donor exposure decreased occurred between 1988 and 1989 while the lowest level was reached in 1989.

From Table 6-3, the total number of infants that are likely to be infected with hepatitis C virus was estimated to be around 49. The number of infants infected who would be still be surviving was estimated to be 18 individuals. The decrease in the estimate per unit risk of HCV was large after 1990 and thus the number of infected and surviving infants decreased as well.

Table 6-3: Estimation of the number of infants infected with HCV and number of survivors with HCV

Years	Estimates of per unit risk for HCV#	Calculated unit exposure risk for HCV in neonates (Mean ± SD)	Number of neonates with HCV infection in the population (n, range)	Estimates for proportion of survival with HCV	Calculated number of neonates surviving in the population with HCV (n, range)
1978	0.00400	0.015 ± 0.025	3.32 (-2.21, 8.84)	0.303	1.01 (-0.67, 2.68)
1979	0.00400	0.020 ± 0.026	6.74 (-2.02, 15.50)	0.314	2.12 (-0.63, 4.87)
1980	0.00400	0.020 ± 0.027	6.78 (-2.37, 15.93)	0.325	2.20 (-0.77, 5.18)
1981	0.00400	0.018 ± 0.019	6.05 (-0.34, 12.43)	0.338	2.04 (-0.11, 4.20)
1984	0.00356	0.021 ± 0.030	7.54 (-3.23, 18.31)	0.375	2.83 (-1.21, 6.87)
1985	0.00310	0.019 ± 0.033	6.46 (-4.76, 17.68)	0.387	2.50 (-1.84, 6.84)
1986	0.00260	0.013 ± 0.016	3.68 (-0.85, 8.21)	0.400	1.47 (-0.34, 3.28)
1987	0.00225	0.011 ± 0.016	2.55 (-1.16, 6.26)	0.412	1.05 (-0.48, 2.58)
1988	0.00195	0.009 ± 0.012	2.11 (-0.70, 4.91)	0.425	0.90 (-0.30, 2.09)
1989	0.00166	0.009 ± 0.015	2.20 (-1.46, 5.86)	0.439	0.97 (-0.64, 2.57)
1990	0.00143	0.007 ± 0.010	1.08 (-0.46, 2.62)	0.468	0.51 (-0.22, 1.23)
1991	0.00017	0.001 ± 0.001	0.16 (0, 0.31)	0.502	0.08 (0, 0.16)
1992	0.00017	0.001 ± 0.001	0.06 (0, 0.13)	0.543	0.03 (0, 0.07)
Total		0.013 ± 0.018	48.73 (-16.50, 102.27)	0.402	17.71 (-6.63, 41.11)

= Taken from "Report from the meeting of the expert panel on Hepatitis C Epidemiology, June 17-18, 1998"

Discussion

In the University of Alberta NICU, there were not many changes during the time period of January 1978 to April 1992 in terms of the number of admissions, mean birthweight and gestational age, in-hospital and overall mortality and length of stay. There is a slight decrease in the percentage of transfusions occurring with any blood product including albumin and IVIG.

Similar trends were noticed for certain variables when the population was divided into infants weighing less than or equal to 1500 grams and those weighing more than 1500 grams. Transfusions in the VLBW infants have not decreased dramatically as seen in the study by Widness and his colleagues. In their study at the University of Iowa Hospital and Clinics, they found that the percentage of infants in the VLBW category who did not require RBC transfusions decreased from 17% in 1982 to 64% in 1993 (Widness et al, 1996). In addition, there was a progressive decline in RBC transfusions and donor exposures occurring concurrently with decreases in mortality rates. Mortality was significantly lower in the VLBW infants than the larger infants but the percentage of infants dying remained the same. However, more than 95% of infants weighing 1000 grams or less in all years received transfusions (Widness et al, 1996). This result was comparable to the results in the present study in that approximately 80% of infants are transfused and are in the VLBW category in each year.

Analysis of single unit exposures and the trend in the amount of blood administered to infants who eventually died was conducted (results not shown here). Certain trends that were observed are as follows:

- Single unit administration of FFP decreased markedly after 1986 and then again after 1989. The percent receiving a single unit of FFP varied from a high of 12.4% in 1984 to a low of 1.6% in 1990.
- For PC, administration of single units decreased after 1985 and 1987. The percent ranged from 1.6% (1992) to 11.8% (1985). After 1985, the percent of single unit exposures dropped from 11.8% to 9.2% while after 1987 the decrease was from 8.1% to 5.9%. The overall decrease in single unit exposures for PC was approximately 86%, which is comparable to the decrease in FFP exposures.
- There was no particular time trend observed for the amount of blood that was administered to neonates who eventually died. The percentages ranged from 2.1% (1992) to 13.0% (1985).

The percentage of neonates transfused with "any blood products except albumin and IVIG" declined in two different years when significant steps were taken to increase the safety of the blood supply. From November 1985, Canada's donor blood supply has been screened for antibodies to HIV and since 1990 routine screening for antibodies to HCV has been performed (Heddle et al, 1997). As a result, hospitals, physicians and nurses became more aware of the risks that were associated with transfusion of blood products especially the risk of transfusion-associated infectious diseases. Significant declines in the percent of neonates transfused dropped noticeably between 1985 and 1986 and again between 1989 and 1990.

The use of blood products such as packed cells and fresh frozen plasma in neonates experienced the sharpest declines for these periods. The proportional decreases for these products were greater than the decline in the percent of neonates transfused. For

packed cells the decrease was approximately 50% while fresh frozen plasma usage declined around 80%.

The figures and trends for whole blood, platelets and albumin were slightly different. Whole blood usage in the latter years after 1980 were almost zero and this is due to the replacement of whole blood with reconstituted blood where red cell concentrates were re-suspended in FFP was used. Reconstituted blood usage became common because it obviated the need for fresh blood, it supplied all the coagulation factors and plasma proteins needed and alleviated concerns about the high plasma potassium and low pH present in stored whole blood (Sacher et al, 1989). Platelet use remained steady as the reasons for its transfusion include to the presence of qualitative and quantitative platelet defects such as the decline in platelet cell counts or the occurrence of thrombocytopenia (Blanchette et al, 1991). However, albumin usage after 1986 increased from zero to almost 52% and this may be due to the fact that it corrects hypovolemia and resuscitates neonates who are in shock in the delivery room (Blanchette et al, 1991; Letsky, 1990). Moreover, albumin undergoes viricidal pasteurization and has a good safety record (Chalmer and Gibson, 1994). However, albumin requires large pools of human plasma for preparation and is expensive to produce (Chalmer and Gibson, 1994).

Donor exposure decrease was clearly evident in the plots of the mean donor to unit exposure for FFP and PC as well as any blood products except for albumin and IVIG. This decrease can be attributed to various changes that may have occurred to limit donor exposure including:

- Prolonging the acceptable age of blood for simple iatrogenic phlebotomy replacement (Donowitz et al, 1989).

- Use of a sterile connecting device to withdraw just what is needed per transfusion making it possible to create many small volume transfusions from a single unit (Donowitz et al, 1989).
- The use of quadruple packs instead of the traditional method of transfusion such as dispensing blood from fresh units of RBCs or pediatric packs, allowing the use of blood from a single donor for multiple transfusions without blood wastage (Donowitz et al, 1989).
- The intra- and post-operative collection, processing and re-infusion of shed red blood cells are additional alternatives (Billman, 1993) for reducing donor exposures in neonates.

Blank and colleagues showed that "booster" or top-up transfusions did not aid in appropriate weight gain or resolve and prevent apnea (Blank et al, 1984). In the present study, decrease in single unit exposures for FFP and PC decrease after 1986 and 1984 respectively. The practice has declined markedly to approximately 85% for both blood products. Thus conservative guidelines for FFP and PC administration was incorporated in the NICU.

Hepatitis C virus is responsible for most cases of hepatitis in multi-transfused children. However, there are few published data regarding the incidence, natural history or associated conditions of HCV infection in children (Bortolotti et al, 1993). Unlike, the United States, Canada did not use surrogate marker screening (antibody to Hepatitis B core antigen and alanine aminotransferase levels) of blood donors as a means of possibly reducing the transmission of non-A, non-B viral hepatitis (Preiksaitis et al, 1998). In addition, the first-generation and second-generation HCV screening test for

antibodies became available in 1990. Thus, transmission of hepatitis C before 1990 could have occurred in these neonates.

The current rate of transfusion-associated hepatitis has not been determined accurately in infants (Strauss, 1991). In this study, the number of babies who may be infected with HCV was estimated with consideration of patient survival. It was estimated that 49 infants or 0.61% of infants would have been infected with hepatitis C and of those about 18 infants or 0.23% of infants would be surviving. The relatively high mortality in this group results from the fact that mortality is especially high among multiply transfused infants in the NICU. The decrease in the estimated transmission of HCV was affected by changes accompanying the introduction of screening tests for HIV that were implemented in 1985, including awareness of the risk that transfusion carried.

In summary, the findings described the changes in transfusion practices in a neonatal intensive care unit. Declines were observed in the percentage of neonates transfused, the types of blood products used, single unit exposures for FFP and PC and the estimated unit exposure risk of HCV. Major changes were linked to the introduction of major screening programs to enhance the safety of the blood supply. The introduction of technological advances and strict transfusion guidelines altered the institution's practices in the NICU and may have contributed to the decrease in donor exposures of neonates. Even though the safety of the blood supply has increased due to innovations, strict donor selection and proper screening tests for various infectious diseases, practitioners should remain cautious in their use of blood products especially in special populations such as neonates.

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Chapter 7

Discussion and Conclusions

The risk factors for neonatal mortality in this study were birthweight, gestational age and transfusion. These findings were similar to those of the Malaysian study, however, transfusion in their study had a protective effect unlike this study (Malaysian Very Low Birth Weight Study Group, 1997). In addition, mortality was worse in infants who weighed less than 1500 grams, were younger than 29 weeks and were transfused with more than 50 units of any blood product except albumin and IVIG. The risk factors for survival were gestational age and transfusion status predicted by a Cox regression model. These findings are of particular significance, as studies assessing the risk factors for mortality in neonates have not been carried out previously.

Most previous studies have dealt with risk factors that predict the need for transfusion or ways to limit unit and donor exposure. Knowledge of particular risk factors for mortality can provide insight into how infants should be assessed and researched especially in terms of transfusion of blood products. For example, this study found that neonates that were VLBW and/or pre-term (less than 29 weeks) received more units of blood compared to their larger and older counterparts. Perhaps this special subgroup of infants could receive recombinant human erythropoietin, which has been shown to safely stimulate erythropoiesis and decrease the requirement for transfusions in selected pre-term infants (Paul et al, 1997). Another intervention to decrease unit exposures of blood products is by increasing the red blood cell mass through placental transfusion by delayed cord clamping in the delivery room especially for premature infants (Kinmond et al, 1993).

Some surprising findings were that survival for infants who receive 50 or more units of any products except albumin and IVIG had a better survival than infants who receive units that range anywhere from two to 49 over a period of time. The reason for this

phenomenon may be that the long-term survival of infants with birthweights of less than 1500 gram continues to improve, which results in an increasing number of infants requiring multiple RBC transfusions (Strauss, 1991). In addition, occasional transfusions are given to infants with birthweights greater than 1500 grams (Strauss, 1991). So a combination of blood products with a receipt of 50 units or more increases the chances of survival due to prolonged stay in the NICU where complications and illness severity resolve as time goes by but requires various and many blood products.

Another surprising find was the amount of blood products that are transfused into babies who eventually die. This percentage was quite high at almost 30%. This means that infants who have died probably received some of the infected blood products. Consideration of this decreased the estimates for the number of infants infected with HCV and probably yielded more accurate numbers.

Assessment of the changes in transfusion practices over the thirteen-year period may also have been helpful decreasing the number of infected infants in the population. After 1985 and 1989, the number of transfused infants and the types of blood products administered decreased drastically. While donor exposure for individual products such as PC and FFP as well as all blood products excluding albumin and IVIG decreased after 1987 and 1988. To eliminate the transmission of infections from donors, blood banks have continuously improved medical screening of blood donors and laboratory testing of donated blood (Strauss, 1991). Thus all of these factors may have contributed to the decrease in unit exposure risk of transfusion-associated infectious diseases.

In this study, based on previous estimates of the incidence of hepatitis C in the general population, estimates of per donor risk of HCV and the number of infected infants was

carried out. In addition, the number of surviving infants with hepatitis C was also computed. This suggested that 49 infants may be infected with an upper confidence limit of 102 infants. Of these, 17 infants are likely to have survived, with and upper limit of 41 infants.

Neonatal mortality and survival are influenced by many causal factors. The speculation and determination of these factors was the purpose of two of the papers. The last paper evaluated the changes that have occurred in transfusion practices and estimated the number of infants infected and surviving with HCV. The complex factors associated with neonatal mortality, transfusion practices and transfusion-associated infectious diseases have a considerable impact on neonates of all weights and ages.

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Appendix 1

Bivariate Analysis for Transfusion

Table : Comparison of those who were transfused with those who were non-transfused for selected risk factors

Characteristics	Transfused		Non-transfused		Odds ratio	95% confidence interval	p-value
	n	%	n	%	OR	95% CI	
Birthweight (grams)							
0 – 500	11	30.6	25	69.4	0.5	0.3, 1.1	0.0760
501 – 750	131	87.3	19	12.7	8.2	5.0, 13.4	0.0000
751 – 1000	269	90.0	30	10.0	10.6	7.2, 15.6	0.0000
1001 – 1500	615	75.1	204	24.9	3.6	3.0, 4.3	0.0000
1501 – 2500	1195	45.6	1424	54.4	1.0	Reference category	
2501 - 4500	1448	36.5	2516	63.5	0.7	0.6, 0.8	0.0000
≥ 4501	21	20.6	81	79.4	0.3	0.2, 0.5	0.0000
Gestational age (weeks)							
20 – 23	12	33.3	24	66.7	0.6	0.3, 1.3	0.2144
24 – 28	508	89.8	58	10.2	11.2	8.5, 14.9	0.0000
29 – 32	802	67.7	383	32.3	2.7	2.3, 3.1	0.0000
33 – 36	1064	43.8	1368	56.3	1.0	Reference category	
37 – 42	1286	34.6	2432	65.4	0.7	0.6, 0.8	0.0000
≥ 43	14	31.1	31	68.9	0.6	0.3, 1.1	0.0940
Gender							
Female	1480	44.0	1880	56.0	0.9	0.8, 0.9	0.0011
Male	2212	47.7	2421	52.3	1.0	Reference category	
Died during follow-up							
Yes	673	75.4	219	24.6	4.2	3.5, 4.9	0.0000
No	3019	42.5	4082	57.5	1.0	Reference category	
In-hospital mortality							
Yes	563	74.0	198	26.0	3.7	3.2, 4.4	0.0000
No	3129	43.3	4103	56.7	1.0	Reference category	
Length of stay (days)							
< 1	90	34.6	170	65.4	1.7	1.3, 2.2	0.0003
1	198	48.4	211	51.6	2.9	2.4, 3.6	0.0000
8 – 14	807	48.3	863	51.7	2.9	2.6, 3.3	0.0000
15 – 30	838	55.0	686	45.0	3.8	3.3, 4.4	0.0000
≥ 31	1065	84.2	200	15.8	16.6	14.0, 19.8	0.0000
2 – 7	694	24.2	2168	75.8	1.0	Reference category	

Appendix 2

Kaplan-Meier Survival Curves

Figure: Overall survival function of the neonatal population

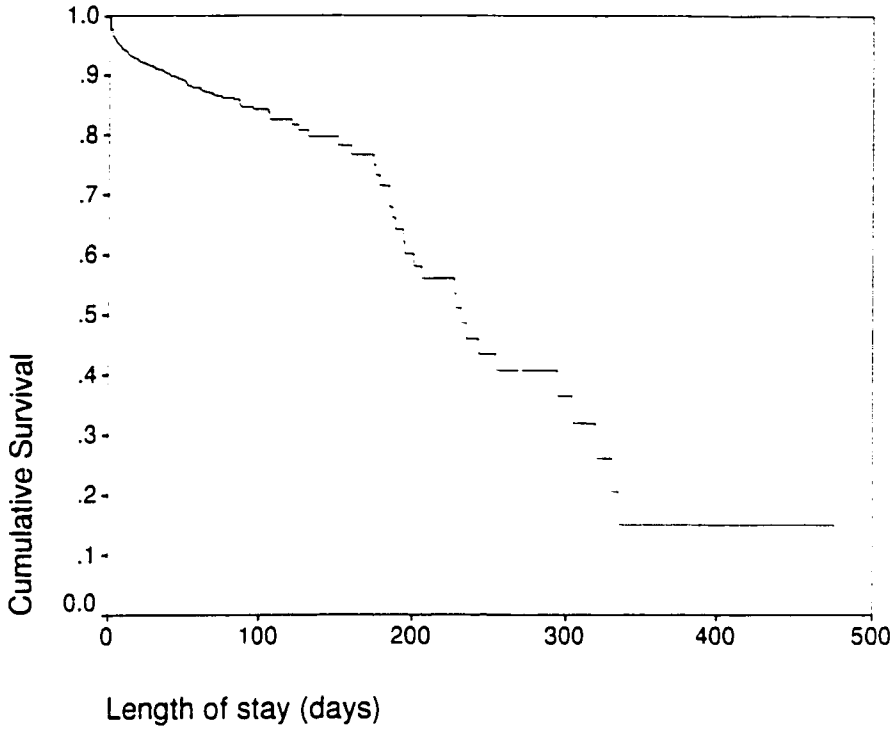


Figure: Survival function for gender

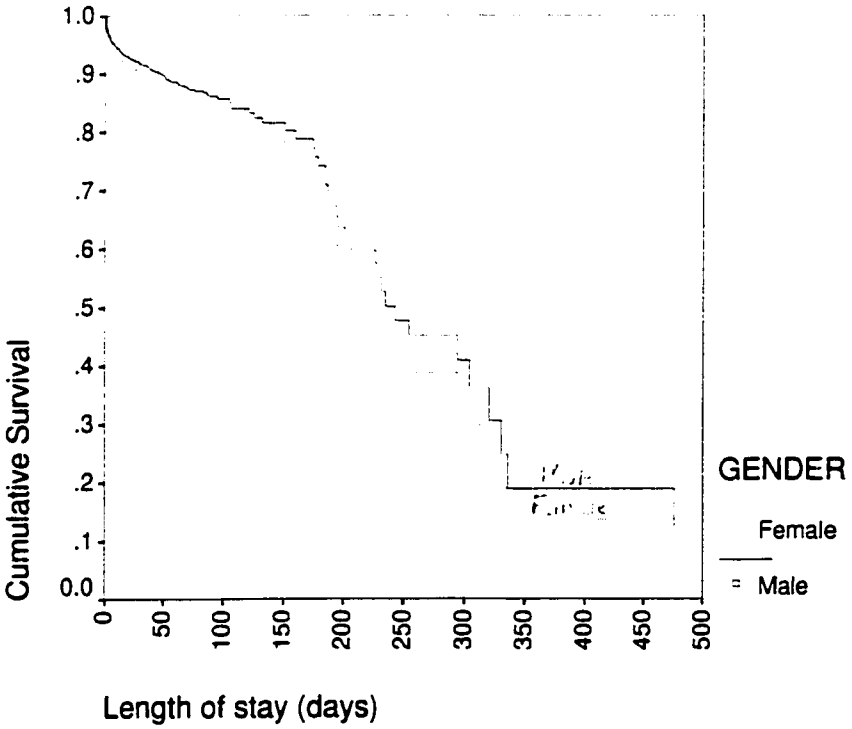


Figure: Survival function for cryoprecipitate unit and donor exposures

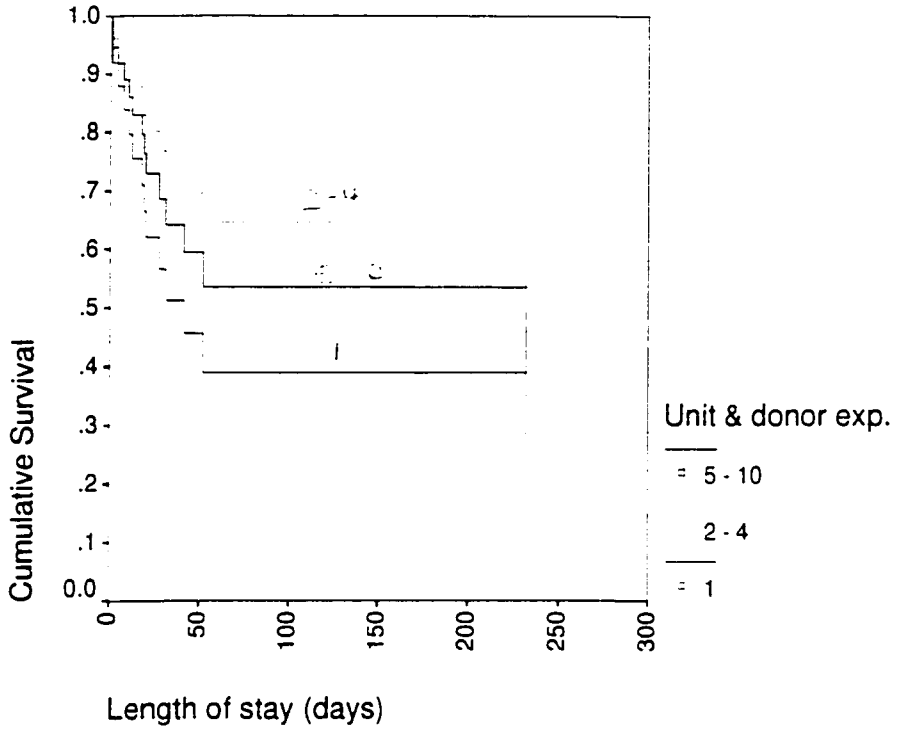


Figure: Survival function for whole blood unit exposures

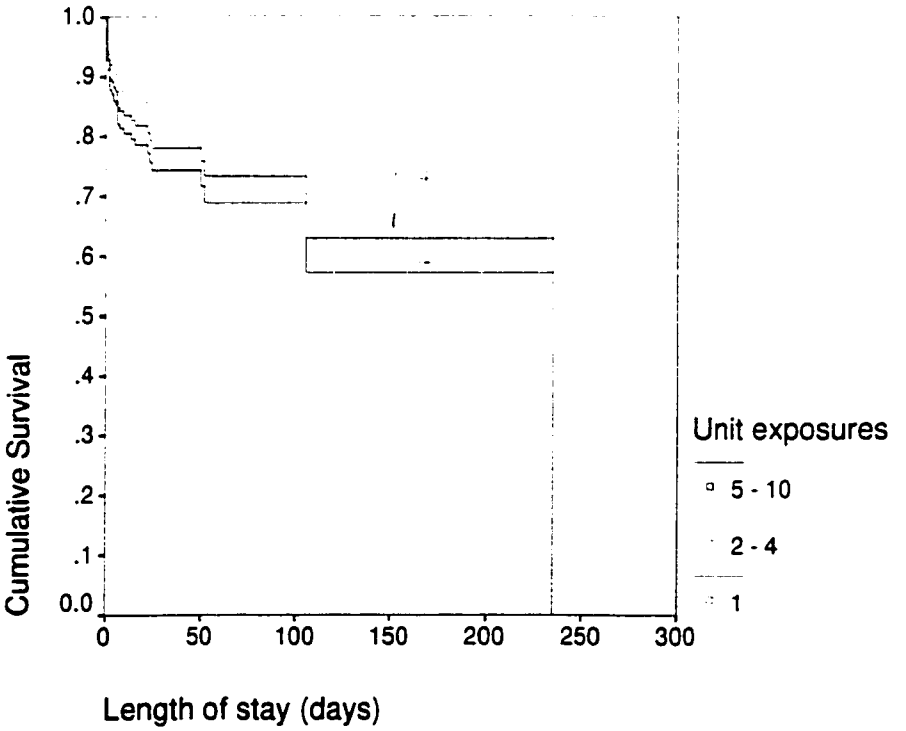


Figure: Survival function for whole blood donor exposures

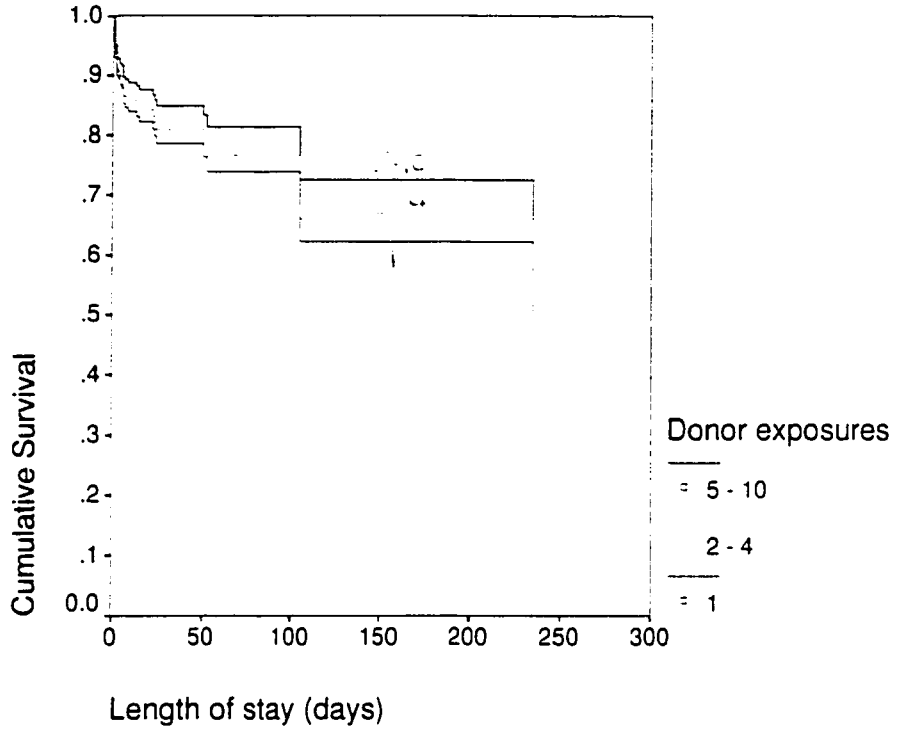


Figure: Survival function for platelet unit exposure

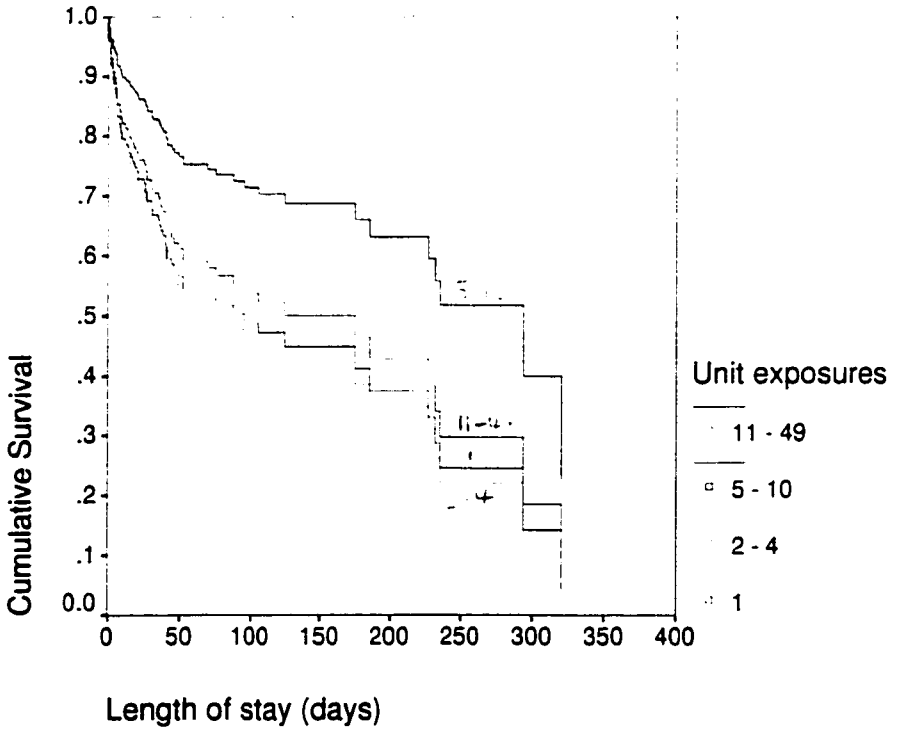


Figure: Survival function for platelet donor exposures

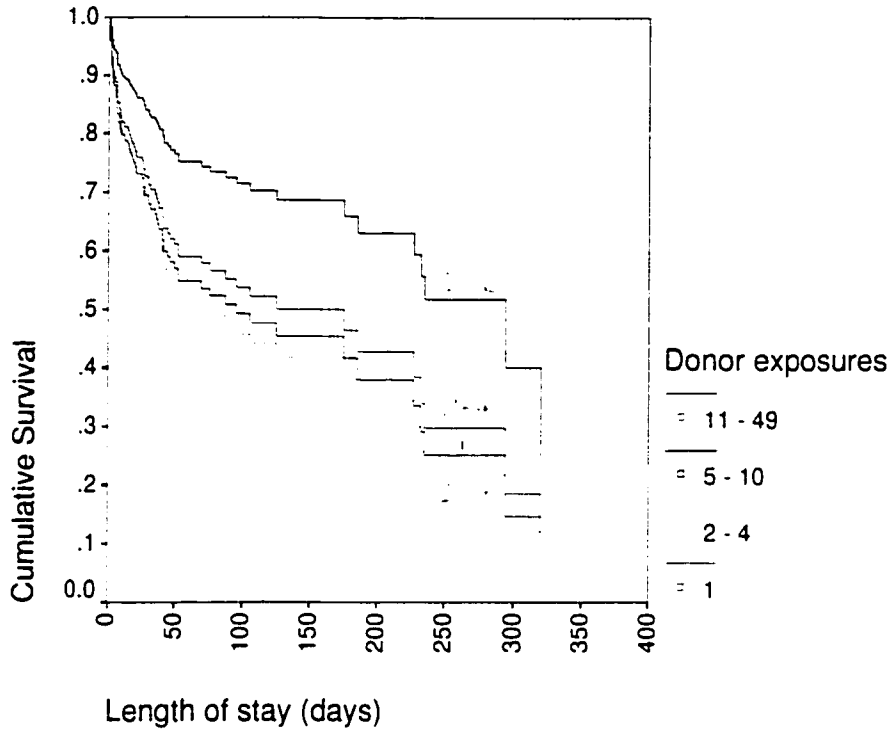


Figure: Survival function for fresh frozen plasma donor exposures

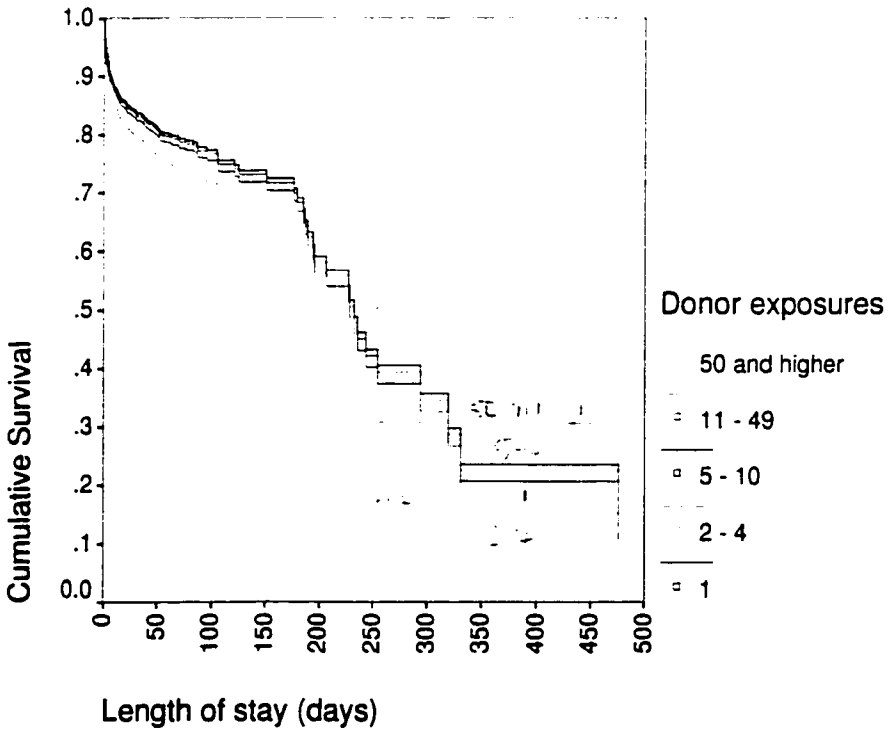


Figure: Survival function for packed cell donor exposures

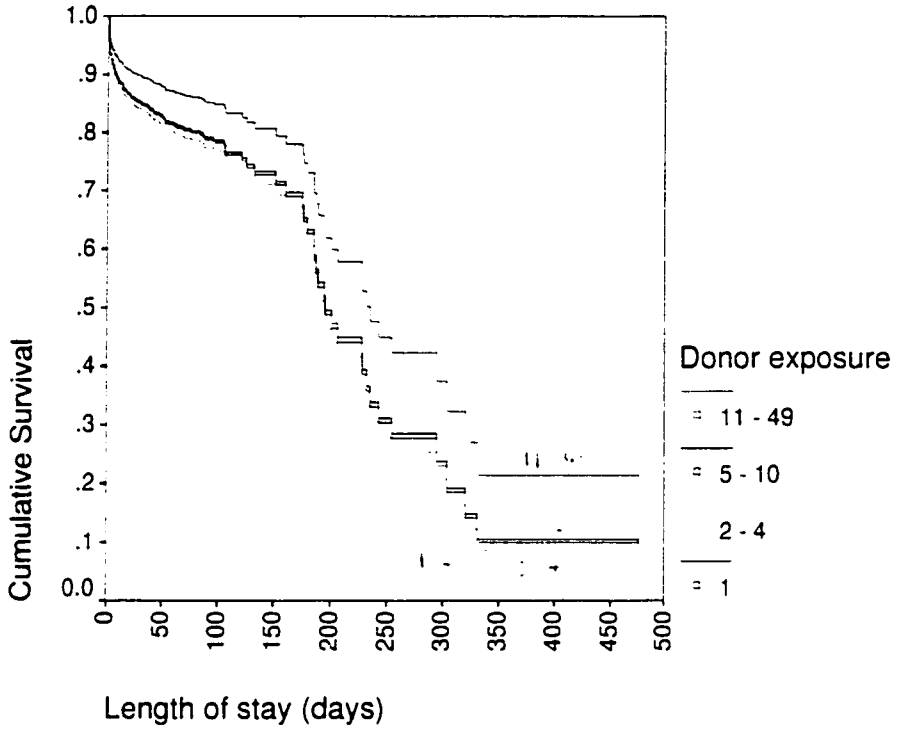


Figure: Survival for donor exposures of blood products except albumin and IVIG

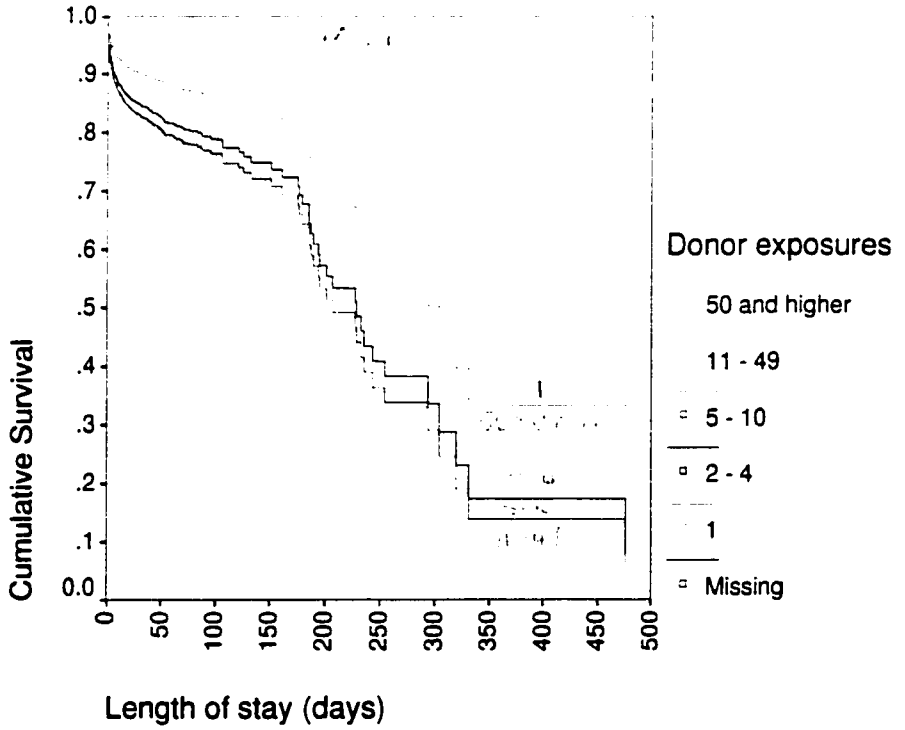
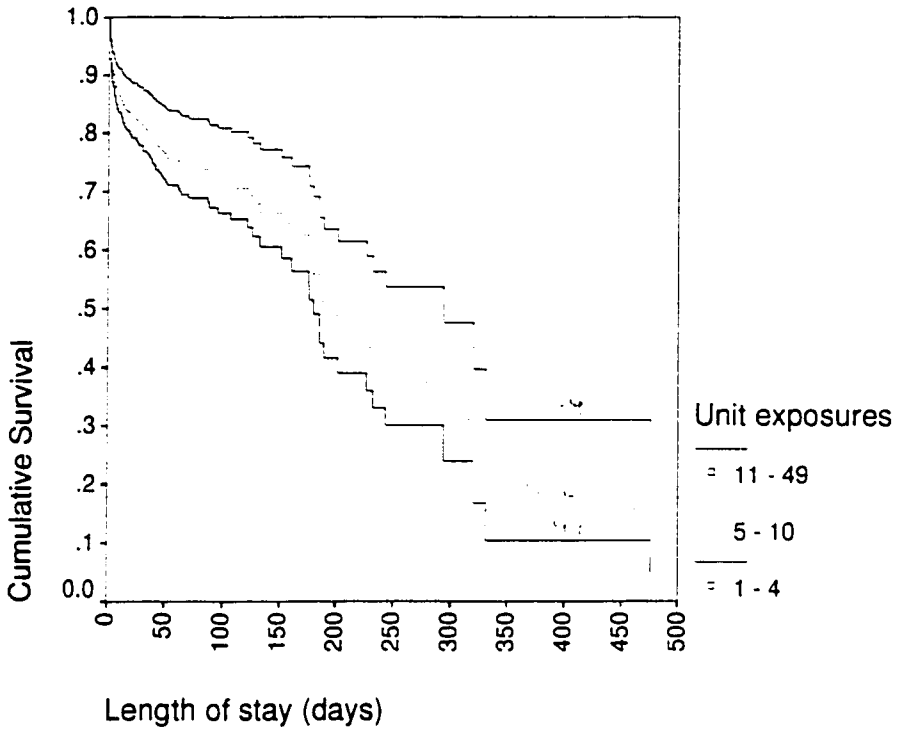


Figure: Survival function for albumin unit exposures



Appendix 3

Exact Cox Regression Modeling for Mortality

Cox Regression

```
    8042  Total cases read
      63  Cases with missing values
     260  Valid cases with non-positive times
       0  Censored cases before the earliest event in a stratum
     323  Total cases dropped
    7719  Cases available for the analysis

Dependent Variable:  NLOS  NUMERIC LENGTH OF STAY

          Events  Censored

             553      7166 (92.8%)

Beginning Block Number 0.  Initial Log Likelihood Function

-2 Log Likelihood    9073.937

Beginning Block Number 1.  Method:  Enter

Variable(s) Entered at Step Number 1..
    GANUM     NUMERIC GESTATIONAL AGE

Coefficients converged after 3 iterations.

-2 Log Likelihood    9014.162

                   Chi-Square     df     Sig
Overall (score)        61.247      1   .0000
Change (-2LL) from
 Previous Block        59.775      1   .0000
 Previous Step         59.775      1   .0000

--------------- Variables in the Equation ----------------

Variable         B       S.E.       Wald  df     Sig        R

GANUM       -.0766      .0098    60.6757   1    .0000   -.0804

                    95% CI for Exp(B)
Variable    Exp(B)      Lower      Upper

GANUM         .9263      .9086      .9443

Covariate Means

Variable          Mean

GANUM          35.8711
```

Cox Regression

```
    8042  Total cases read
      63  Cases with missing values
     260  Valid cases with non-positive times
       0  Censored cases before the earliest event in a stratum
     323  Total cases dropped
    7719  Cases available for the analysis

Dependent Variable:  NLOS  NUMERIC LENGTH OF STAY

          Events  Censored

             553      7166 (92.8%)

Beginning Block Number 0.  Initial Log Likelihood Function

-2 Log Likelihood    9073.937

Beginning Block Number 1.  Method:  Enter

Variable(s) Entered at Step Number 1..
    GANUM     NUMERIC GESTATIONAL AGE
    TRANS     TRANSFUSED

Log likelihood converged after 4 iterations.

-2 Log Likelihood    8816.072

                   Chi-Square     df     Sig
Overall (score)       233.455      2   .0000
Change (-2LL) from
 Previous Block       257.866      2   .0000
 Previous Step        257.866      2   .0000

-------------- Variables in the Equation ---------------

Variable         B       S.E.       Wald  df      Sig        R

GANUM       -.0340      .0097    12.3142   1    .0004   -.0337
TRANS       1.6138      .1321   149.3317   1    .0000    .1274

                    95% CI for Exp(B)
Variable    Exp(B)      Lower      Upper

GANUM         .9665      .9483      .9851
TRANS        5.0218     3.8766     6.5053

Covariate Means

Variable          Mean

GANUM          35.8711
TRANS            .4659
```

Appendix 4

Trends in Transfusion

Table: Description of Transfusion Practice Trend for Neonates over the Years

Years	Total	Two admits	Transfused with all blood products		Non transfused		Transfused with blood products excluding Albumin and IVIG		Donor exposures excluding Albumin and IVIG	Unit exposures excluding Albumin and IVIG	Deaths		Deaths in infants who were transfused	
	n	n	n	%	n	%	n	%	n	n	n	%	n	%T
1978	459	1	222	48.4	237	51.8	221	48.1	850	1010	51	11.1	42	19.0
1979	642	1	337	52.5	305	47.5	337	52.5	1658	1969	72	11.2	56	16.6
1980	679	11	339	49.9	340	50.1	339	49.9	1691	1927	96	14.1	67	19.8
1981	664	4	338	50.9	326	49.1	336	50.6	1528	1629	79	11.9	53	15.7
1984	701	7	360	51.4	341	48.6	359	51.2	2102	2364	91	13.0	60	16.7
1985	629	6	342	54.4	287	45.6	340	54.1	2038	2362	78	12.4	68	19.9
1986	676	5	284	42.0	392	58.0	283	41.9	1452	1636	88	13.0	64	22.5
1987	673	6	239	35.5	434	64.5	232	34.5	1164	1342	70	10.4	53	22.2
1988	732	0	262	35.8	470	64.2	234	32.0	1109	1426	63	8.6	45	17.2
1989	712	5	334	46.9	378	53.1	244	34.3	1316	1794	75	10.5	63	18.9
1990	619	2	269	43.5	350	56.5	154	24.9	787	1015	57	9.2	44	16.4
1991	577	1	268	46.5	309	53.6	157	27.2	720	983	49	8.5	39	14.6
1992	230	0	98	42.6	132	57.4	63	27.4	296	378	23	10.0	19	19.4
Total	7993	49	3692		4301		3299		16711	19835	892		673	

Total = Total number of admissions.
Two admits = Babies who were admitted twice to the Neonatal Intensive Care Unit
Transfused with all blood products = Babies transfused with products such as Packed Cells (PC), Fresh Frozen Plasma (FFP), Platelets (PLT), White Blood Cells (WBC), Whole Blood (WhBl), Cryoprecipitate (CRYO), Albumin (Alb) and Immunoglobulin (IVIG).
Deaths = Frequency and percentage of babies who died over the years from the total.
%T = Percentage of babies who die from the total number transfused with all the products.

Table: Description of the different product types used for neonates during the time period from January 1978 to April 1992

Years	WBC^		CRYO#		Whole blood*		Platelets (PLT)*		FFP*		PC*		Mean ± SD for all blood products*	
	n	%	n	%	n	%	n	%	n	%	n	%	Unit Exposure	Donor Exposure
1978	2	0.4	2	0.4	75	16.3	4	0.9	100	21.7	161	35.0	4.6 ± 7.4	3.9 ± 6.3
1979	0		0		75	11.7	13	2.0	185	28.8	290	45.1	5.9 ± 7.9	4.9 ± 6.6
1980	1	0.1	1	0.1	21	3.0	12	1.7	188	27.2	300	43.5	5.7 ± 7.8	5.0 ± 6.8
1981	0		0		4	0.6	16	2.4	213	31.9	293	43.9	4.9 ± 5.1	4.6 ± 4.8
1984	0		6	0.8	15	2.1	26	3.7	224	31.6	311	43.9	6.6 ± 10.1	5.9 ± 8.4
1985	0		6	0.9	7	1.1	32	5.0	214	33.7	297	46.8	7.0 ± 13.0	6.0 ± 10.5
1986	1	0.1	8	1.2	5	0.7	37	5.4	185	27.2	249	36.6	5.8 ± 7.2	5.1 ± 6.3
1987	2	0.3	1	0.1	2	0.3	23	3.4	159	23.4	203	29.9	5.8 ± 8.4	5.0 ± 7.1
1988	0		1	0.1	4	0.5	13	1.8	140	19.1	199	27.2	6.1 ± 8.3	4.7 ± 6.2
1989	0		5	0.7	7	1.0	29	4.0	120	16.7	227	31.7	7.4 ± 13.8	5.4 ± 9.1
1990	0		2	0.3	1	0.2	23	3.7	57	9.2	141	22.7	6.6 ± 8.9	5.1 ± 7.2
1991	0		3	0.5	6	1.0	19	3.3	44	7.6	145	25.1	6.3 ± 10.4	4.6 ± 7.9
1992	0		1	0.4	1	0.4	8	3.5	33	14.3	53	23.0	6.0 ± 8.6	4.7 ± 6.8
Total	6		36		223		255		1862		2869			

WBC = White Blood Cells; CRYO = Cryoprecipitate; FFP = Fresh Frozen Plasma; PC = Packed Cells
All blood products is a combination of WBC, CRYO, Whole blood, PLT, FFP and PC
^ p-value = 0.133
# p-value = 0.012
* p-value < 0.001

Table: Trend for single unit exposures for cryoprecipitate, whole blood, platelets, fresh frozen plasma and red blood cells from January 1978 to April 1992

Type of blood product	Years													Total
	1978	1979	1980	1981	1984	1985	1986	1987	1988	1989	1990	1991	1992	
Cryoprecipitate*														
n			1		3	2	3	1		3	1		1	15
%			6.7		20.0	13.3	20.0	6.7		20.0	6.7		6.7	100
Whole Blood^														
n	57	50	12	4	5	3	2		2	2	1	2		140
%	40.7	35.7	8.6	2.9	3.6	2.1	1.4		1.4	1.4	0.7	1.4		100
Platelets#														
n	4	9	7	12	10	11	14	7	5	10	11	10	3	113
%	3.5	8.0	6.2	10.6	8.8	9.7	12.4	6.2	4.4	8.8	9.7	8.8	2.7	100
Fresh Frozen Plasma^														
n	53	76	72	89	93	75	79	66	59	41	12	17	16	748
%	7.1	10.2	9.6	11.9	12.4	10.0	10.6	8.8	7.9	5.5	1.6	2.3	2.1	100
Red Blood Cells^														
N	66	112	106	113	117	118	92	81	59	48	31	43	16	1002
%	6.6	11.2	10.6	11.3	11.7	11.8	9.2	8.1	5.9	4.8	3.1	4.3	1.6	100

* p is non-significant
^ $p \leq 0.005$
# $p = 0.052$

Table: Mean ± standard deviation of unit exposures for cryoprecipitate, whole blood, platelets, fresh frozen plasma, red blood cells and albumin for neonates weighing less or greater than 1500 grams from January 1978 to April 1992

Type of blood product	Years												
	1978	1979	1980	1981	1984	1985	1986	1987	1988	1989	1990	1991	1992
Cryoprecipitate$													
≤ 1500 grams					4.0 ± 5.2						3.0	2.0	
> 1500 grams	4.0 ± 2.8		1.0		4.3 ± 4.9	4.0 ± 4.0	5.0 ± 4.1	1.0	2.0	1.8 ± 1.3	1.0	2.5 ± 0.7	1.0
Whole Blood*													
≤ 1500 grams	1.3 ± 0.7	1.6 ± 1.1	1.5 ± 0.7	1.0					1.0	1.0		1.0	
> 1500 grams	1.3 ± 0.7	1.5 ± 0.9	1.9 ± 1.4	1.0	2.4 ± 1.6	1.6 ± 0.5	2.4 ± 1.7	4.0 ± 2.8	1.7 ± 0.6	3.2 ± 1.9	1.0	2.0 ± 0.7	2.0
Platelets$													
≤ 1500 grams	1.0	1.0	1.5 ± 0.7	1.0	2.7 ± 2.7	2.2 ± 2.2	1.6 ± 1.3	6.5 ± 7.5	1.7 ± 1.2	1.8 ± 0.8	2.8 ± 2.6	3.3 ± 4.4	3.2 ± 2.7
> 1500 grams	1.0	1.5 ± 0.7	1.9 ± 1.9	1.3 ± 0.5	2.8 ± 2.5	4.1 ± 5.1	3.2 ± 2.3	4.1 ± 5.6	2.7 ± 1.4	3.6 ± 3.3	2.8 ± 1.7	2.9 ± 2.9	2.3 ± 1.2
FFP^													
≤ 1500 grams	4.3 ± 4.6	5.4 ± 6.1	3.7 ± 3.5	2.7 ± 1.6	4.7 ± 7.1	4.2 ± 4.5	3.7 ± 3.8	3.8 ± 4.8	6.3 ± 6.6	5.0 ± 4.5	5.2 ± 6.4	6.5 ± 9.0	5.7 ± 6.8
> 1500 grams	3.1 ± 5.0	3.2 ± 3.6	3.7 ± 6.3	2.5 ± 2.3	3.5 ± 4.4	5.0 ± 11.6	3.4 ± 3.7	3.3 ± 3.6	2.9 ± 3.3	5.4 ± 12.2	5.2 ± 5.9	3.8 ± 5.5	2.8 ± 2.9
RBCs#													
≤ 1500 grams	5.9 ± 5.9	7.4 ± 7.0	6.6 ± 6.5	6.0 ± 5.2	8.2 ± 8.8	6.3 ± 5.7	5.0 ± 4.4	4.4 ± 5.3	5.8 ± 6.2	5.0 ± 4.5	6.4 ± 6.4	6.8 ± 7.7	5.4 ± 5.5
> 1500 grams	2.5 ± 3.4	2.7 ± 2.8	2.6 ± 2.6	2.3 ± 1.9	2.8 ± 3.1	2.8 ± 3.4	2.6 ± 3.3	2.7 ± 3.0	3.3 ± 3.7	4.5 ± 8.9	3.2 ± 3.3	2.8 ± 2.5	3.0 ± 2.8
Albumin*													
≤ 1500 grams				2.0 ± 1.5	1.2 ± 0.4	1.2 ± 0.6	1.8 ± 2.0	2.6 ± 3.3	2.9 ± 2.1	5.1 ± 4.2	7.2 ± 7.6	7.3 ± 8.0	5.5 ± 4.8
> 1500 grams	1.0	1.5 ± 0.7	1.5 ± 0.7	1.0	1.3 ± 0.5	1.0	2.0 ± 1.5	2.6 ± 3.8	3.1 ± 4.5	3.5 ± 4.8	3.4 ± 3.6	3.4 ± 3.5	3.1 ± 2.9

$ p is non-significant, * $p < 0.001$, ^ $p \leq 0.005$, # $p < 0.01$

Table: Mean ± standard deviation of donor exposures for cryoprecipitate, whole blood, platelets, fresh frozen plasma (FFP) and red blood cells (RBCs) for neonates weighing less or greater than 1500 grams from January 1978 to April 1992

Type of blood product	Years												
	1978	1979	1980	1981	1984	1985	1986	1987	1988	1989	1990	1991	1992
Cryoprecipitate$													
≤ 1500 grams					4.0 ± 5.2						3.0	2.0	
> 1500 grams	4.0 ± 2.8		1.0		4.3 ± 4.9	4.0 ± 4.0	5.0 ± 4.1	1.0	2.0	1.8 ± 1.3	1.0	2.5 ± 0.7	1.0
Whole Blood*													
≤ 1500 grams	1.1 ± 0.4	1.2 ± 0.5	1.5 ± 0.7	1.0					1.0	1.0		1.0	
> 1500 grams	1.2 ± 0.7	1.3 ± 0.6	1.0 ± 1.0	1.0	2.0 ± 0.9	1.6 ± 0.5	2.4 ± 1.7	4.0 ± 2.8	1.3 ± 0.6	3.0 ± 1.7	1.0	1.8 ± 0.5	2.0
Platelets$													
≤ 1500 grams	1.0	1.0	1.5 ± 0.7	1.0	2.7 ± 2.7	2.2 ± 2.2	1.6 ± 1.3	6.3 ± 7.3	1.7 ± 1.2	1.8 ± 0.8	2.8 ± 2.6	3.2 ± 4.4	3.2 ± 2.7
> 1500 grams	1.0	1.5 ± 0.7	1.9 ± 1.9	1.3 ± 0.5	2.7 ± 2.3	4.1 ± 5.2	3.2 ± 2.3	4.1 ± 5.6	2.7 ± 1.4	3.6 ± 3.3	2.8 ± 1.7	2.7 ± 2.9	2.3 ± 1.2
FFP$													
≤ 1500 grams	4.1 ± 4.1	5.4 ± 5.9	3.6 ± 3.3	2.6 ± 1.6	4.0 ± 5.1	3.9 ± 3.9	3.4 ± 3.4	3.2 ± 3.6	5.2 ± 5.1	3.9 ± 3.5	4.3 ± 5.2	4.5 ± 6.7	3.9 ± 4.4
> 1500 grams	3.0 ± 4.9	3.1 ± 3.5	3.6 ± 6.0	2.5 ± 2.2	3.0 ± 3.5	4.0 ± 8.5	2.9 ± 2.8	2.8 ± 2.7	2.4 ± 2.5	4.2 ± 9.0	3.7 ± 3.9	2.6 ± 3.0	2.2 ± 2.2
RBCs^													
≤ 1500 grams	4.5 ± 4.4	5.5 ± 5.0	5.2 ± 5.1	5.4 ± 4.7	7.5 ± 7.8	5.6 ± 5.1	4.4 ± 4.0	3.7 ± 4.2	4.6 ± 4.6	4.0 ± 3.4	5.1 ± 5.0	5.2 ± 5.8	4.6 ± 4.6
> 1500 grams	2.1 ± 2.8	2.1 ± 2.0	2.1 ± 1.9	2.0 ± 1.7	2.5 ± 2.5	2.4 ± 2.7	2.2 ± 2.8	2.4 ± 2.6	2.2 ± 2.3	2.6 ± 4.4	2.3 ± 2.6	1.7 ± 1.3	2.1 ± 2.7

$ p is non-significant, * $p < 0.001$, ^ $p = 0.051$

Appendix 5

Unit and Donor Exposure Computations

Table: Comparison of those transfused babies who died during follow-up with those who survived for unit and donor exposure of various blood products

	Died		Survived	
	Mean ± SD unit exposure	**Mean ± SD donor exposure**	**Mean ± SD unit exposure**	**Mean ± SD donor exposure**
Product types and their exposures				
White blood cells (WBC)	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0
Cryoprecipitate (CRYO)	2.6 ± 3.2	2.6 ± 3.2	4.2 ± 3.4	4.2 ± 3.4
Whole blood	1.8 ± 1.4	1.5 ± 1.0	1.6 ± 1.0	1.4 ± 0.8
Platelets (PLT)	3.3 ± 4.2	3.3 ± 4.1	2.5 ± 2.4	2.5 ± 2.3
Fresh frozen plasma (FFP)	4.9 ± 8.7	4.0 ± 6.7	3.6 ± 4.8	3.2 ± 3.9
Packed cells (PC)	5.3 ± 6.8	3.9 ± 4.7	3.6 ± 4.3	3.0 ± 3.6
All blood products	9.2 ± 14.0	7.2 ± 10.7	5.3 ± 7.5	4.6 ± 6.3
Albumin	5.7 ± 6.5		3.3 ± 4.0	

All blood products = Combination of WBC, CRYO, Whole blood, PLT, FFP and PC
Unit Exposure = Number of units received by the transfused baby
Donor Exposure = Number of donors that the baby was exposed to during the product transfusion
The values for both unit and donor exposures was same due to the small sample size for the particular product.

Table: Comparison of those who died during follow-up with those who survived for selected blood products

Selected blood products	Died		Survived		Odds ratio	95% confidence interval	p – value
	n	%	n	%	OR	95% CI	
Non-Transfused	219	2.7	4082	51.1	1.0		Reference category
Cryoprecipitate							
1	11	61.1	4	22.2	51.3	16.2, 162.3	0.0000
2 – 4	4	22.2	8	44.4	9.3	2.8, 31.2	0.0003
5 – 10	3	16.7	6	33.3	9.3	2.3, 37.5	0.0017
Total	18	50.0	18	50.0			
Whole Blood							
1	34	63.0	106	62.7	6.0	4.0, 9.0	0.0000
2 – 4	16	29.6	57	33.7	5.2	3.0, 9.3	0.0001
5 – 10	4	7.4	6	3.6	12.4	3.5, 44.4	0.0000
Total	54	24.2	169	75.8			
Platelets							
1	42	37.5	71	50.0	11.0	7.4, 16.5	0.0000
2 – 4	53	47.3	49	34.5	20.2	13.4, 30.4	0.0000
5 – 10	9	8.0	21	14.8	8.0	3.6, 17.6	0.0000
11 – 49	8	7.1	1	0.7	149.1	18.6, 1197.5	0.0000
Total	112	44.1	142	55.9			

Figure 1: Means for Proportion of donor to unit exposures for cryoprecipitate

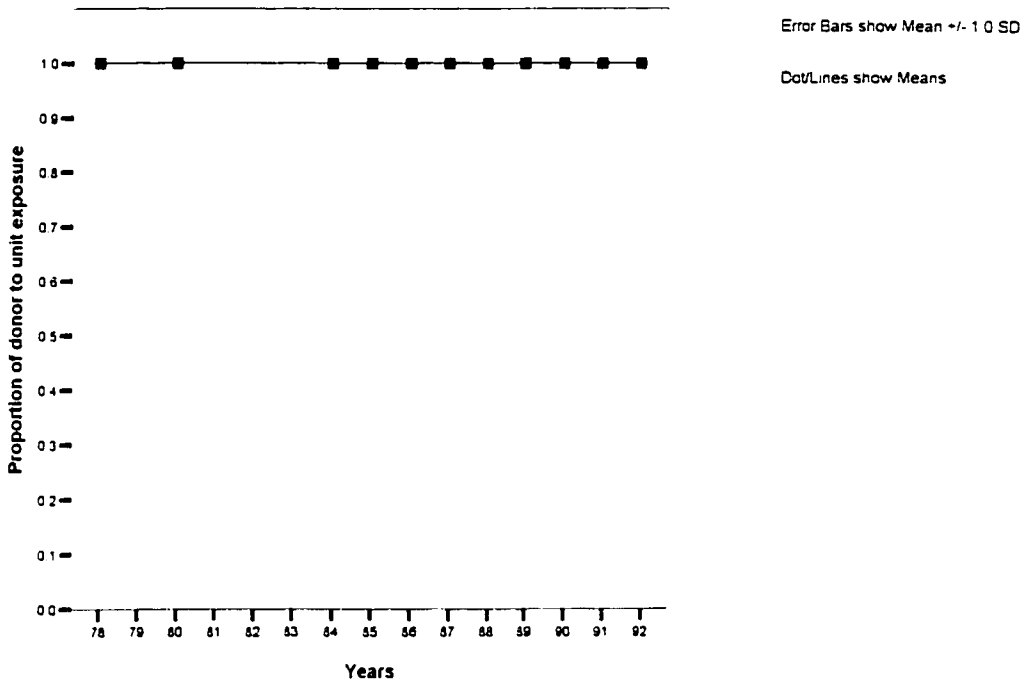


Figure 2: Means for Proportion of donor to unit exposures for whole blood

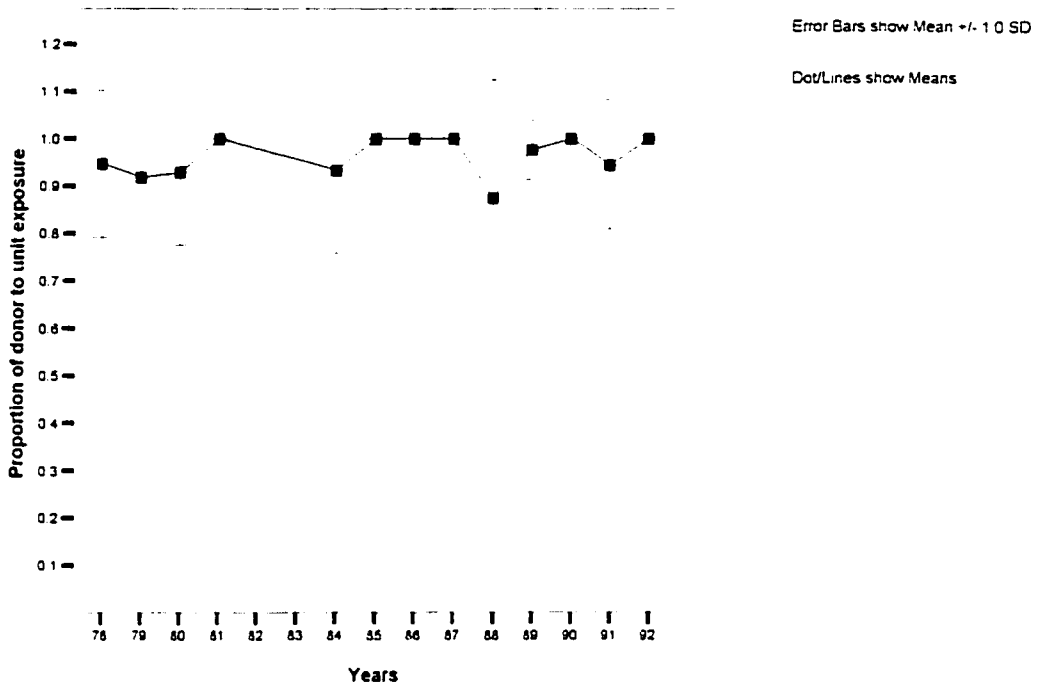


Figure 3: Means for Proportion of donor to unit exposures for platelets

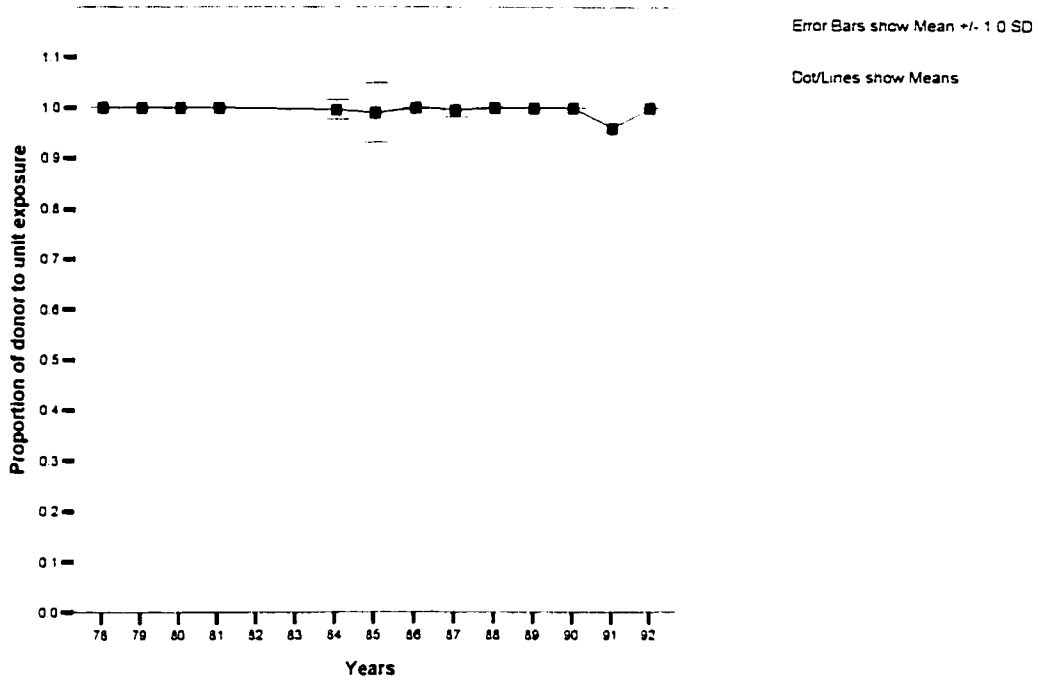


Figure: Usage of cryoprecipitate from January 1978 to April 1992

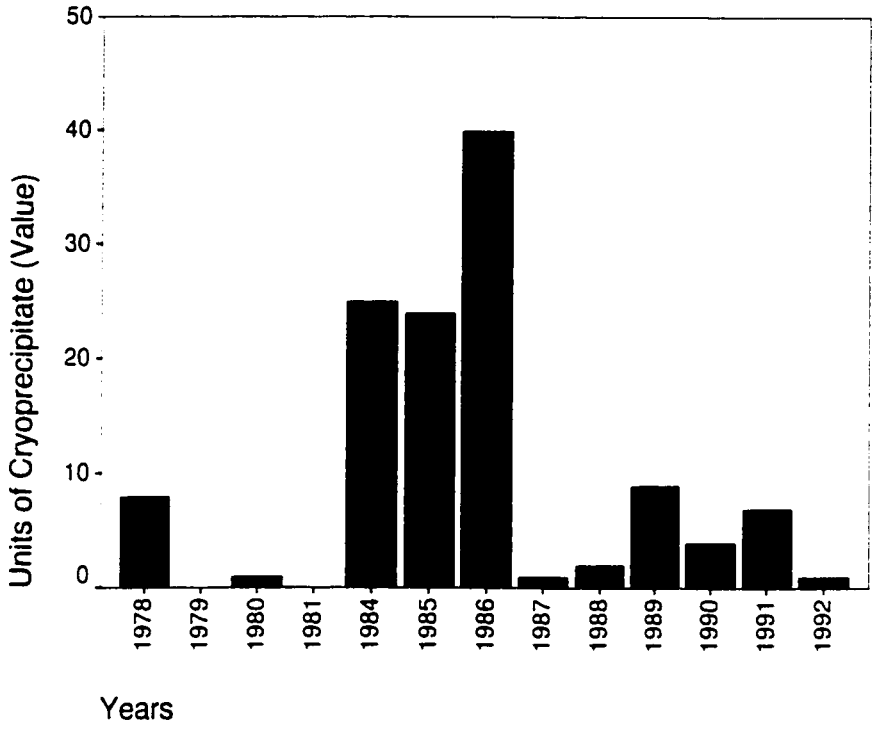


Figure: Usage of whole blood from January 1978 to April 1992

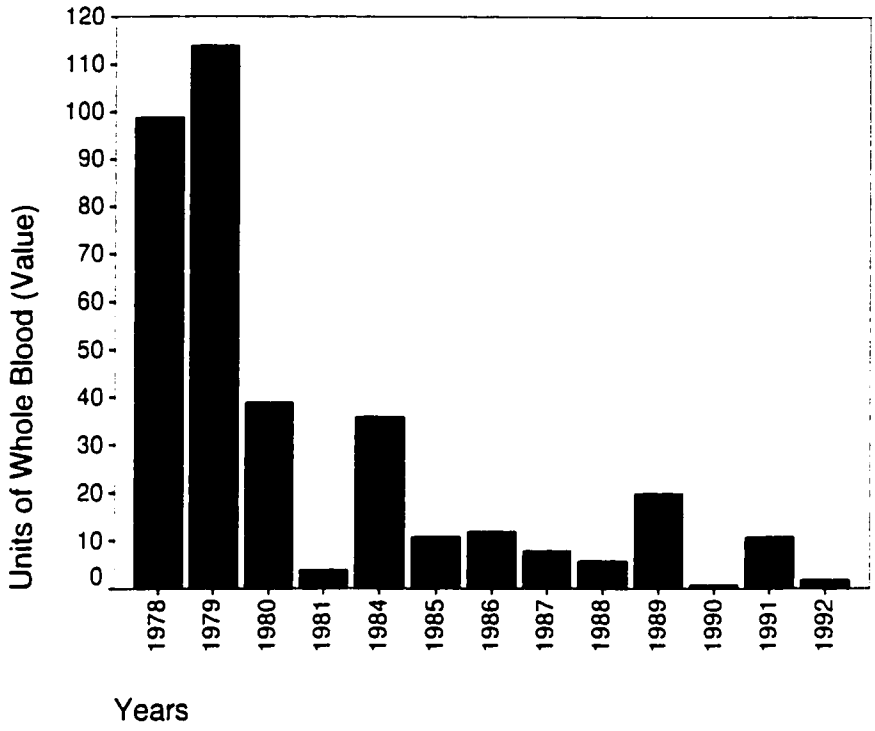


Figure: Usage of platelets from January 1978 to April 1992

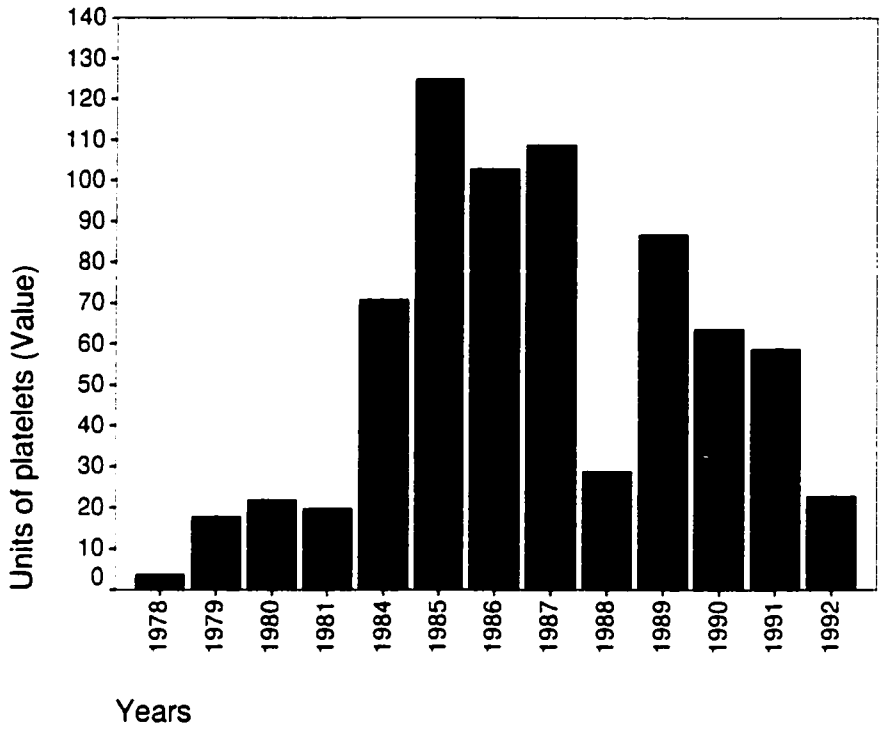


Figure: Usage of fresh frozen plasma (FFP) from January 1978 to April 1992

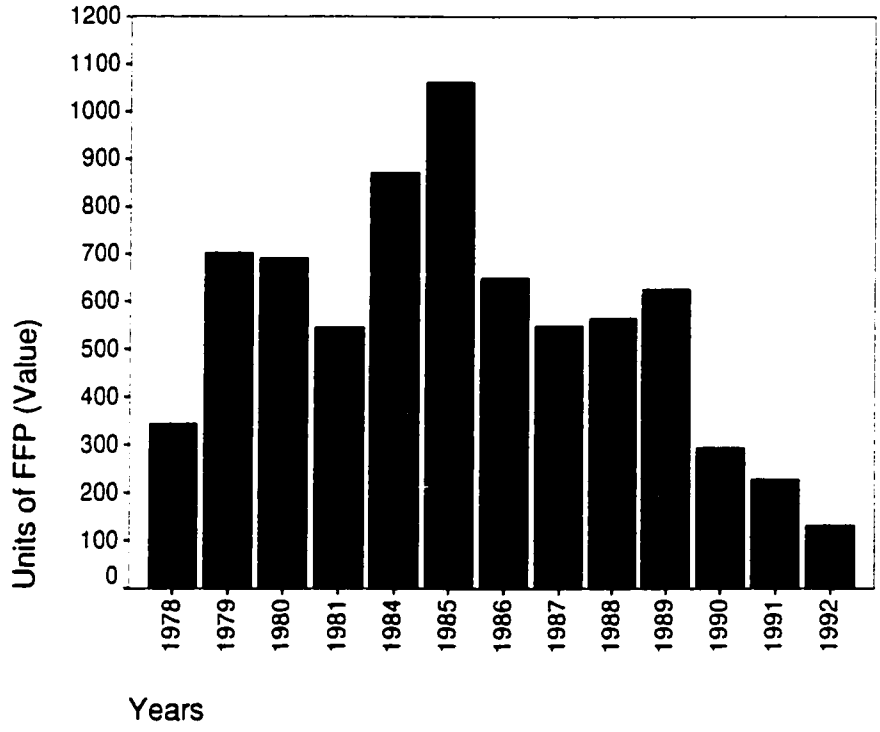


Figure: Usage of red blood cells (RBCs) from January 1978 to April 1992

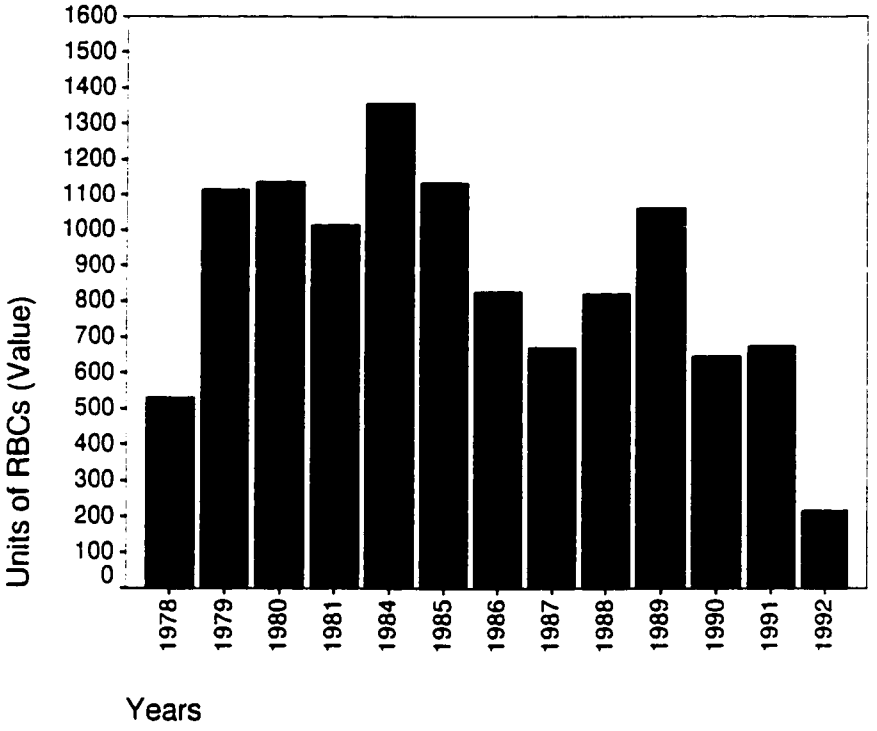


Figure: Usage of albumin from January 1978 to April 1992

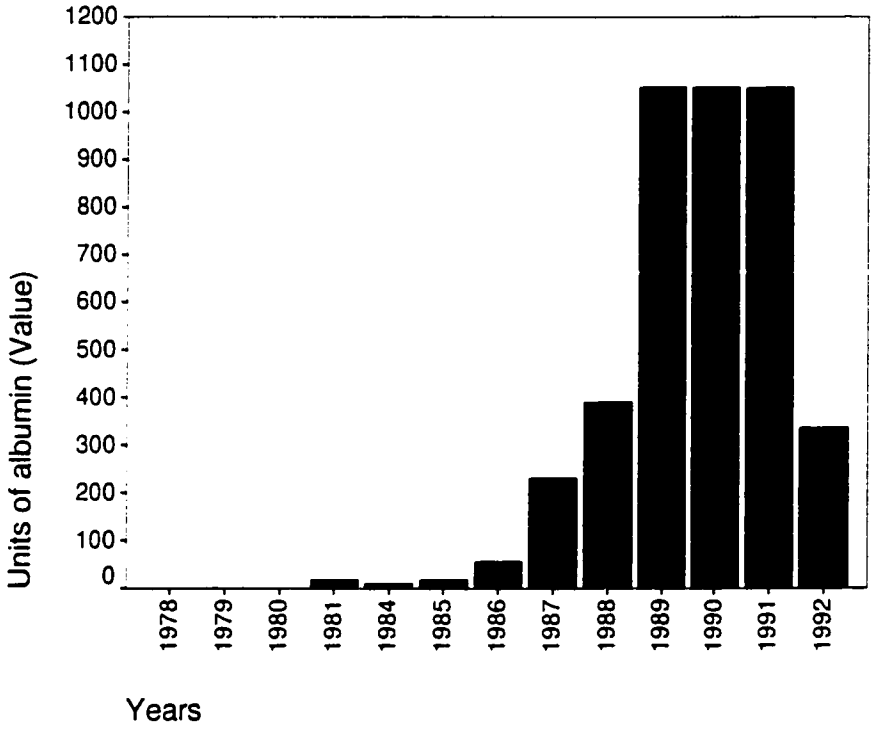


Figure: Usage of all blood products except albumin and IVIG from January 1978 to April 1992