

My name is Christine Holschlag. I have worked at the American Red Cross since January 12<sup>th</sup> 2004 as a phlebotomist. I am here to comment on Bill no. 5451.

On Section 1 part B, we would like to see a minor adjustment. There is no reference to a licensed professional overseeing the transfusion of citrate, saline, and biologics into a donor. While I am not trained in this particular procedure nor a registered nurse, I am aware that serious reactions can occur as referenced in the 'Complications of Donor Apheresis'. While states may differ, California operates apheresis procedures only by registered nurses. We are not asking for that ruling in Connecticut but, for a registered nurse to be trained in all apheresis procedures and oversee such procedures.

On Section 1 part C, a registered or licensed practical nurse required at every blood drive would be instrumental in ensuring donor, recipient, and worker safety. Prior to 2006, we had only registered nurses overseeing blood drives. The nurse was qualified to answer complex medical questions, assess a presenting donor in question, and tend to any medical emergency that arose. The Red Cross has only 1/3<sup>rd</sup> of those nurses now and we are frequently running blood drives with no licensed personnel.

On Section 2, an employee receiving bonuses off of blood production is truly an ethical concern. We are not selling cars, we are manufacturing a drug to be transfused into a patient. When you base someone's income on the quantity of a product and not the quality, the product may be jeopardized. Blood drives are frequently overbooked and workers feel pressured to close the drive on time and possibly rush the process. While this may be a business, this is not a place for production incentives. How about safety incentives?

On Section 3, we have submitted a journal article from the Journal of the American Medical Association on the increased adverse affects in teens donating blood. This bill brought to my attention that we don't ask for parental consent when 17 yr olds donate blood despite the fact they are minors. So, I suppose we would rather the bill required a parental consent requirement if the donor were a minor whether the age be 16 or 17.



# Complications of Donor Apheresis

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A decreasing blood donor pool in the presence of increasing blood transfusion demands has resulted in the need to maximally utilize each blood donor. This has led to a trend in the increasing use of automated blood collections. While apheresis donation shares many reactions and injuries with whole blood donation, because of the differences, unique complications also exist. Overall, evidence in the literature suggests that the frequency of reactions to apheresis donation is less than that seen in whole blood donation, though the risk of reactions requiring hospitalization is substantially greater. The most common apheresis-specific reaction is hypocalcemia due to citrate anticoagulation, which, while usually mild, has the potential for severely injuring the donor. Other reactions to apheresis donation are uncommon (e.g., hypotension) or rare (e.g., air embolism). More worrisome, and in need of additional study, are the long-term effects of apheresis donation. Recent evidence suggests that repeated apheresis platelet donations may adversely effect thrombopoiesis as well as bone mineralization. Granulocyte donation has also been implicated in unexpected long-term consequences. *J. Clin. Apheresis* 21: 132–141, 2006. © 2005 Wiley-Liss, Inc.

**Key words:** granulocyte donation; platelet donation; plasma donation; citrate toxicity; hypocalcemia; air embolism; G-CSF; thrombocytopenia

## INTRODUCTION

With the trend toward maximal utilization of blood donors in these times of a decreasing donor pool and expanding blood usage, there is a shift toward automated blood collections. These collection methods share many of the same reactions and injuries seen with whole blood donation but also have unique complications due to the collection method and the frequency at which donation can occur. This article provides an overview of the frequency and severity of reactions to apheresis donation in comparison to those seen with whole blood donation, a discussion of the common and uncommon reactions seen with apheresis donation, and a discussion of the potential long-term consequences of donation.

## REACTIONS TO APHERESIS DONATION

The frequency of acute reactions among donors undergoing apheresis procedures was found by McLeod et al. to be 2.18% in a multi-institutional study [1]. In comparison, in a review of reactions among whole blood donors, Newman reported an overall reaction rate to whole blood donation of 11 to 21% [2]. The frequencies of different types of reactions reported by McLeod and Newman are presented in Table I for comparison. As with the overall reaction rate, the frequencies of the reactions observed with apheresis donation were less than that seen with

whole blood donation. As with whole blood donation, McLeod et al. found that first time donors were more likely to have reactions than repeat donors.

Reactions were found to be more frequent among platelet donors (12%) than either plasma (5.9%) or granulocyte donors (9.4%). The authors hypothesized that this was due to a greater frequency of first time donors in the plateletpheresis group. McLeod et al. [1] also noticed that the instrument used for the collection influenced reaction rates. Donors collected with the Fenwal CS3000 had fewer reactions than those collected with the COBE Spectra or Haemonetics instruments. The authors postulated that this was due to a lower citrate infusion rate with the Fenwal CS3000 that produced fewer citrate reactions. In addition, the CS3000 cannot perform single-needle apheresis collection procedures while the other instruments could. It was felt that the larger extracorporeal volumes seen with the single-needle procedures might have contributed to hypotensive reactions [1].

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TABLE I. Reaction Rates Among Apheresis [1] and Whole Blood [21] Donors

Reaction	Apheresis donations (%)	Whole blood donations
Hematoma or pain	1.15	9-16
Citrate toxicity	0.4	NA
Mild vasovagal	0.05	2-5
Vasovagal with syncope	0.08	0.1-0.3

A second study by Despotis et al. [3] looking at reactions to apheresis donations (platelet and leukocyte donations) at a single institution found a similar overall reaction rate of 0.81%. These authors determined the rate of very serious reactions, those requiring hospitalization, to be 0.01% (2 out of 19,736 donations) [3]. This rate is 20 times greater than that reported to occur with allogeneic whole blood donation (1 out of 198,119 donations, 0.0005%) [4]. It, therefore, appears that while the overall rate of reactions in apheresis donors is less than that seen in whole blood donation, the risk of more severe reactions, those requiring hospitalization, is greater.

Among all reactions, Despotis et al. [3] found associations between citrate and hypotensive reactions and donor weight, female gender, and the collection instrument used. For venipuncture related complications, only female gender was associated as a risk factor. In this study [3], an interesting relationship was noted with regard to citrate reactions and the instrument used for the collection. Despotis et al. noted that the relationship between donor weight and citrate reactions was different when comparing the COBE Spectra and the Fenwal CS3000. Donors with lower weights had a higher probability of citrate reactions on the Fenwal CS3000 while those with higher weights had a higher probability on the COBE Spectra. The authors of this study [3] felt that this was due to the methods by which these instruments determine the anticoagulant infusion rate.

## CITRATE TOXICITY

### Hypocalcemia

Citrate is used as the primary anticoagulant in donor apheresis procedures. The anticoagulant effect of citrate results from its ability to chelate calcium ions resulting in the calcium ions being unavailable to participate in biological reactions such as the coagulation cascade. Within the apheresis instrument, plasma citrate concentrations reach 15 to 24 mmol/L, lowering the calcium ion concentration below 0.2 to 0.3 mmol/L, the level necessary for clotting to occur [5]. This level of anticoagulation requires the infusion of approximately 500 mL of ACD-A solution and it would be expected that the infusion of this volume of

solution into a donor would result in a calcium ion concentration of 0.2 mmol/L, a level incompatible with life. This does not occur, however, for a number of reasons. First, when blood returns from the apheresis instrument to the donor, the citrate present in the blood is diluted throughout total extracellular fluid, not just the intravascular space. In addition, the liver, kidneys, and muscles rapidly metabolize citrate, releasing the bound calcium [5]. The body also responds to the decrease in ionized calcium by increasing parathyroid hormone levels with mobilization of calcium from skeletal stores as well as increased absorption by the kidneys [6]. Interestingly, this compensatory mechanism may be limited with intact parathyroid hormone levels reaching their maximum within 30 min of the start of collection without a subsequent increase despite a continued decline of ionized calcium [7]. A final mechanism that compensates for the effects of citrate is that there also appears to be mobilization of ionized calcium bound to serum albumin [8].

Despite compensatory mechanisms, citrate infusion can result in the decrease in ionized calcium levels to a point where symptoms develop in the donor. In a study of the effects of citrate on apheresis platelet donors, Bolan et al. found an average fall in ionized calcium of 33% from baseline [7]. The result of such a decrease in ionized calcium is that the excitability of nerve membranes increases to the point where spontaneous depolarization can occur [5]. This produces the signs and symptoms of citrate toxicity including perioral paresthesias, acral paresthesias, shivering, light-headedness, twitching, and tremors. In addition, some patients also experience nausea and vomiting. As the ionized calcium levels fall further, these symptoms may progress to carpopedal spasm, tetany, and seizure [5]. It is, therefore, important to elicit the presence of the early symptoms from the donor so that interventions can occur prior to the more severe symptoms. Hypotension may also be seen with citrate reactions [9] and may be due to the depressed myocardial function as well as to vascular smooth muscle relaxation [10].

In addition to the symptoms described above, prolongation of the QT interval on electrocardiogram and fatal arrhythmia have been reported [5,11]. Laspina et al. reported prolongation of the QT interval in 76 platelet donors examined during collection procedures [11]. While no adverse events occurred, the authors recommended that apheresis donors should be screened for a family history of long QT syndrome or sudden cardiac death in order to avoid those donors who many have inherited this disorder and be at risk for fatal arrhythmia [11].

Factors that have been found to influence the rate of citrate reactions in donor and therapeutic apheresis



include alkalosis due to hyperventilation [5], the type of anticoagulant solution used with ACD-A having more reactions than ACD-B [12], the rate of infusion of the anticoagulant solution [5], the amount of citrate infused [5], and the donor's serum albumin level prior to the start of the collection procedure [8]. It has also been reported that intermittent flow hemapheresis procedures tend to have a greater frequency of citrate reactions, as there is a higher rate of citrate infusion when the separation chamber is emptied, as compared to continuous apheresis procedures.

The method by which an instrument calculates the dose of anticoagulant also influences the rate of reactions among certain donor subgroups [3]. The COBE Spectra bases its rate of infusion on the donor's blood volume that is calculated by the instrument based upon donor height, weight, and gender. This calculation may overestimate the blood volume in females and obese individuals, resulting in a relative overdose of citrate in these donor populations [3]. The Fenwal CS3000 determines the dose of anticoagulant based upon the blood draw rate. As a result, females with low body weights could receive a relative overdose of citrate as their blood volume is not considered [3].

The treatment of citrate reactions is relatively simple when the reactions are identified early. The treatment includes slowing the re-infusion rate to allow for dilution and metabolism of the citrate, increasing donor blood to citrate ratio to decrease the amount of citrate infused, giving oral calcium in the form of calcium antacids, and giving intravenous calcium [5].

The administration of oral calcium carbonate and its effects on citrate toxicity have recently been examined by Bolan et al. [8,13] These authors found that the administration of 2 g of calcium carbonate was associated with a statistically significant reduction in the severity of paresthesias [13]. Physiologically, this dose was also associated with the greatest improvement in ionized and total calcium levels among the doses examined (1, 2, and 4 g) [8]. While improving paresthesias, in multivariate analysis, the oral administration of calcium was not associated with a reduction in overall symptom development and did not effect the occurrence of more severe symptoms [13].

The administration of intravenous calcium, in the form of calcium gluconate or calcium chloride is usually not necessary in donor procedures and, therefore, has not been studied in this setting. In hematopoietic progenitor cell (HPC) collections, the continuous infusion of either calcium gluconate or calcium chloride has been found to prevent hypocalcemic symptom development [14,15] with calcium chloride maintaining higher ionized calcium levels

[15]. In a comparison with a continuous infusion of calcium gluconate, prophylactically at the start of HPC collection, or at the time of symptom development, continuous infusion maintained higher calcium levels with insignificant changes seen in the other two modes of administration [16].

Continuous infusion should not be necessary in normal apheresis donation. When IV supplementation is necessary, such as in severe reactions, the usual dose of intravenous calcium is 10 ml of 10% calcium gluconate IV infused over 10 to 15 minutes. Too rapid of an infusion can result in hypotension and is to be avoided [17].

### Hypomagnesemia

Magnesium, just as calcium, is a divalent cation and, as a result, is also bound by citrate. Magnesium is second in concentration only to calcium among divalent cations in the blood and is involved in a number of physiologic processes. Infusion of citrate in the setting of plateletpheresis has been found to decrease ionized magnesium by 30 to 40% [7,18]. Ionized magnesium levels have been shown to fall more rapidly than ionized calcium levels during citrate infusion with a more prolonged recovery [18]. Hypomagnesemia can induce signs and symptoms similar to hypocalcemia including muscle spasms, muscle weakness, decreased vascular tone, and impaired cardiac contractility. In addition, hypomagnesemia can also impair calcium and potassium homeostasis, inhibiting the release of parathyroid hormone when markedly decreased [18]. As a result, individuals with low magnesium levels prior to undergoing apheresis with citrate anticoagulation may exhibit signs and symptoms of citrate toxicity due to hypomagnesemia and not hypocalcemia. These symptoms may be unresponsive to the administration of calcium supplementation.

### Other Acute Effects of Citrate

The metabolism of citrate consumes hydrogen ions and results in a rise in the blood pH of donors during apheresis platelet collections [7]. Metabolic alkalosis has been reported to occur in therapeutic apheresis patients with renal disease who cannot adequately excrete bicarbonate [19] and in those receiving replacement fluids containing citrate, such as fresh frozen plasma [20]. As donors should have normal renal function and will not be receiving as great a citrate load, significant metabolic alkalosis should not occur [19].

The rise in blood pH seen with this metabolic alkalosis also results in a shift in hydrogen ions from



intracellular locations in an attempt to compensate. This produces a concurrent flux of potassium into these cells to maintain electrical neutrality resulting in a fall in serum potassium levels. Bolan et al. noted a 6% decline in serum potassium levels among apheresis platelet donors [7].

### HYPOTENSIVE REACTIONS

Hypotension during apheresis collections can result from a number of factors including intravascular volume depletion, vasovagal reactions, citrate reactions, severe allergic reactions, and air embolism. In some cases, hypotension may be multifactorial.

With intravascular volume depletion, hypotension results due to the removal of blood that fills the extracorporeal circuit. This is characterized by increased vascular tone and cardiac output as the sympathetic nervous system attempts to compensate for the hypovolemia [5]. Increased cardiac output occurs through an increase in heart rate as well as increased cardiac contractility. These reactions are not common among hemapheresis donors as regulatory restrictions limit the extracorporeal volume to 10.5 mL/Kg [21] with most modern instruments having an extracorporeal volume well below this, except in the smallest of donors.

Another mechanism causing hypotension during apheresis procedures is the vasovagal reaction. In this reaction, hypovolemia results in a decrease in blood pressure. The compensatory response for this volume depletion is to increase sympathetic nervous system output with physiologic compensation as previously described. During a vasovagal reaction, however, parasympathetic output that normally counteracts sympathetic output increases, resulting in a slowing of heart rate and decreased vascular tone [5]. This results in hypotension. Factors that have been associated with vasovagal reactions in whole blood donors include younger age, low weight, first time donation, and inattentive collection staff [2].

Tomita et al. examined the incidence of vasovagal reactions among apheresis donors and whole blood donors at the same collection center. They found the incidence of vasovagal reactions among female apheresis donors and female whole blood donors to be 1.25 and 4.17%, respectively. The rate among male donors was 0.83 and 0.99%, respectively [22]. The rate among apheresis donors was substantially greater than that reported by other authors [1,3] although an explanation was not apparent from the data reported. Tomita et al. noted that the incidence of vasovagal reactions increased with age among apheresis donors, unlike what has been reported with whole blood donors. This increasing incidence was especially true in women [22]. Tomita et al. hypothesized that the

higher incidence in women and the increasing frequency with age were related to a lower circulating blood volume in these donor groups with a resulting greater percentage of the donor's blood being within the extracorporeal circuit during collection. This resulted in a greater drop in blood pressure during collection leading to more vasovagal reactions. Tomita et al. also noted that the incidence of these reactions increased with increasing cycles during a collection. Based upon this, they theorized that hypocalcemia may also be involved in the onset of vasovagal reactions in apheresis donors [22].

Hypovolemic and vasovagal reactions are treated similarly. The procedure should be temporarily interrupted and a fluid bolus should be infused. If the reaction is due to hypovolemia, the blood pressure should increase and the pulse rate should decrease in response to this intervention. If the reaction is due to a vasovagal reaction, this may not occur. Additional treatments for vasovagal reactions include placing the donor in Trendelenburg position (head down below the level of the heart), applying cold compresses to the forehead and neck, and reassuring the donor [5].

### ALLERGIC REACTIONS

Allergic reactions result from the release of vasoactive substances from mast cells and basophils when IgE antibodies bound to their surface bind the antibody's target antigen. The release of these substances produces a variety of symptoms by causing contraction of smooth muscle, increased vascular permeability, and vasodilatation. Mast cells and basophils can also be activated by complement-derived factors such as C3a and C5a, which can be produced by a variety of mechanisms including antigen-IgG interactions. These types of reactions can range from mild urticarial reactions to life-threatening anaphylactic reactions. Signs and symptoms of these reactions include pruritus, urticaria, erythema, flushing, angioedema, upper airway obstruction, lower airway obstruction, hypotension, shock, nausea, vomiting, and diarrhea [23].

Allergic reactions have been reported in donors undergoing collections including platelet, plasma, and granulocyte donors. Among platelet and plasma donors, reactions to ethylene oxide used to sterilize the disposable sets have been described [24,25]. These reactions have occurred predominantly in donors who have donated by apheresis numerous times. It is thought that during the procedures, ethylene oxide present within the plastic binds to proteins within the plasma with these serving as carrier molecules. The ethylene oxide becomes a hapten resulting in an immune response to the ethylene oxide bound to the serum protein and production of IgE antibodies. In most of the apheresis



donors who experienced allergic phenomenon, IgE antibodies to ethylene oxide were identified [25]. The reactions ranged from urticaria, flushing and periorbital edema [25] to an anaphylactic reaction consisting of wheezing, flushing, swelling of the lips, and hypotension [24]. The overall rate of the reactions in one study was 1.0% of platelet donors. Reactions were most frequent with one plateletpheresis instrument examined in that study, the Fenwal CS3000 as compared to the Haemonetics V-50. The authors of the study felt that this was due to the fact that at the start of processing with the CS3000, a mixture of saline and anticoagulant that was used to prime the disposable set was infused into the patient. This was not the case with the V-50 where the priming solution was diverted to a waste bag. It was postulated that this difference resulted in a bolus of ethylene oxide to the donor resulting in the reactions [25]. Attempts to prevent these reactions among donors have included double priming the disposable set in order to remove any ethylene oxide present as well as using the oldest kits, with presumably the least amount of ethylene oxide left, for these donors.

Allergic type reactions have also been reported among granulocyte donors. While ethylene oxide reactions could also occur in this group, another possible mechanism could be exposure to hydroxyethyl starch. Granulocyte donors are exposed to hydroxyethyl starch, either low molecular weight or high molecular weight, in order to enhance red cell sedimentation. While these substances are poor immunogens and have not been able to induce antibody formation, allergic reactions have occurred in the setting of HES use in hemapheresis [26] and as a volume expander [27]. The mechanism behind the production of these reactions is thought to be due to the ability of HES to activate the alternate complement cascade. This would result in the production of C3a and C5a, both of which can cause mast cell and basophil histamine release [26]. Reactions reported to occur with HES include mild urticarial reactions as well as severe reactions with respiratory and cardiac arrest. The rate of reactions in a study of patients receiving HES for volume expansion was 0.085% with severe (anaphylactic) reactions occurring in 0.006% [27]. Reactions have occurred with both high molecular weight (hetastarch) [27] and low molecular weight (pentastarch) [28] HES. Because of this risk, Dutcher et al. recommended that people with a history of any allergies be excluded from granulocyte donations [26].

In all donor reactions, the procedure should be stopped. The subsequent treatment of allergic reactions depends upon their severity. Simple reactions, such as urticaria, can be treated with oral antihistamines. For anaphylactic reactions, vascular access should be

maintained using saline. With less severe reactions, epinephrine 0.3 to 0.5 mg can be given subcutaneously with the dose being repeated every 20 to 30 minutes for up to three doses. In addition, aminophylline 6 mg/Kg can be given for bronchospasm. This loading dose should be followed by an infusion of 0.5 to 1 mg/Kg/hour. Volume expansion with normal saline or lactated Ringer's solution can be given for hypotension. Oxygen should be given for respiratory distress. For severe reactions, epinephrine 0.5 mg can be given intravenously, with repeated dosing every 5 to 10 minutes. Dopamine can also be given for hypotension unresponsive to volume infusion. The airway must also be protected and endotracheal intubation may be indicated [23]. Obviously, the best course of action is to avoid such reactions. Donors who have experienced such reactions should be deferred from future apheresis donation.

## BLEEDING

### Thrombocytopenia

A platelet donor typically experiences an acute fall in platelet count of 20 to 29% following donation [29-31]. Among females, this decrease tends to be greater [32,33]. Interestingly, the fall in platelet count does not correlate with the yield of the plateletpheresis procedure as more platelets are collected than anticipated due to the mobilization of platelets from the spleen during collection [29]. Dettke et al. found the time required for a donor to return to baseline following a platelet donation to be four days in males with a delay in increase of thrombopoietin levels and a corresponding delay in return to normal platelet counts in females [33]. In donors undergoing alternate day collections, platelet count and apheresis yields have been shown to return to baseline levels by day 10 of collection with stable counts and yields with subsequent collections [34]. A rebound elevation in platelet count with increased platelet yield following repeat procedures has been reported [31]. In donors with low platelet counts (150,000 to 180,000/mL), plateletpheresis using prolonged collection times in order to achieve adequate platelet product yields demonstrated no clinically significant problems in 291 procedures, despite post-procedure platelet counts as low as 69,000/mL [32]. The results of these studies indicate that platelet counts return to normal levels promptly following plateletpheresis, even in those undergoing repeated procedures, and that bleeding complications are uncommon.

In granulocyte collections, platelets and significant numbers of red blood cells are also present in the leukapheresis product. Typically, a drop in hemato-



crit of 7% and a fall in platelet count of 22% occurs after each granulocyte donation. This fall is due to the loss of these cells in the product as well as the dilutional effects of volume expansion caused by the HES used during the procedure [35]. In donors stimulated with G-CSF, however, there appears to be a greater decrease in platelet count [36]. Healthy donors receiving G-CSF for 10 days typically have a decline in platelet count starting at day 8 with significant differences in counts at days 10 and 11. The mechanism behind this effect is uncertain and may represent changed platelet distribution, decrease platelet production, or increased intravascular volume [37]. In addition, recovery of platelet count also appears to be prolonged requiring 7 to 10 days for recovery among stem cell donors versus 4 to 6 days among platelet donors [38].

### Hydroxyethyl Starch

The use of HES, either as volume replacement or as a sedimenting agent, has also been associated with changes in coagulation factor levels. Both high and low molecular weight HES produce a prolongation of the partial thromboplastin time (PTT) and a decrease in fibrinogen levels when infused. This is thought to result from the dilutional effects produced as the colloidal action expands intravascular volume. High molecular weight, but not low molecular weight HES, is also associated with decreases in factor VIII activity, factor VIII antigen, and Von Willebrand factor (vWF) antigen as well as prolongation of bleeding time [39]. It is thought that this last effect is a result of the decrease in vWF antigen levels and may represent an acquired Von Willebrand disease-like state. Because of these changes, a risk of coagulopathy exists with the use of high molecular weight HES as a sedimenting agent. This risk appears to be dose dependent. In the setting of volume expansion in critical care, the maximum dose of HES beyond which such complications can occur is 20 mL/Kg/24-hour period. Doses up to 3,600 mL, however, have been given in the critical care setting without difficulty [40]. The danger in hemapheresis procedures is that multiple collections may be necessary over consecutive days. Since HES, especially high molecular weight HES, has a long half-life, this may result in an accumulation.

### Removal of Coagulation Factors

Plasma donation could theoretically result in bleeding if donation resulted in the removal of coagulation factors faster than the donor's synthetic ability. Studies of plasma donors have not supported this concern [41,42].

**TABLE II. Relative Contraindications to Granulocyte Mobilization Regimens [37,47]**

Medication	Condition
Corticosteroids	Hypertension Diabetes Peptic ulcer disease
G-CSF	Inflammatory conditions Gout Risk factors for thrombosis

### Anticoagulant Induced Bleeding

Concern occasionally arises as to whether citrate concentrations within the donor will cause bleeding. As stated, in order to anticoagulate blood, calcium levels less than 0.2 to 0.3 mmol/L must be achieved. This level is achieved in the hemapheresis instrument but not in the donor. Such a low ionized calcium level is incompatible with life.

### REACTIONS TO G-CSF AND CORTICOSTEROIDS USED IN GRANULOCYTE COLLECTION

G-CSF can be used alone or in combination with steroids to enhance granulocyte collection yields. These medications can cause a number of side effects. Common side effects associated with corticosteroids include headache, flushing, insomnia, euphoria, palpitations, epigastric acidity, and hyperglycemia [43]. Common side effects of G-CSF administration include bone pain, myalgias, arthralgias, headache, fever, chills, gastrointestinal discomfort, paresthesias, chest pain, chills, and fatigue [43]. The side effects seen with G-CSF are common, occurring in 90% of allogeneic donors receiving G-CSF for hematopoietic progenitor cell mobilization [44]. They are usually mild and treated symptomatically, such as the administration of mild analgesics for the bone pain and headache. The side effects of G-CSF tend to be dose related [44,45] with the exceptions being nausea/vomiting and headache, with the former being more common in women and the latter being more common in those under 35 years old [45]. More significant side effects have been reported with G-CSF including splenic rupture, retinal hemorrhage, acute iritis, gouty arthritis, and thrombotic events [37,43]. These are felt to represent exacerbation of underlying donor illnesses and donors should be evaluated for these in determining suitability for donation (Table II). A report has also appeared in which an allogeneic peripheral blood hematopoietic progenitor cell donor experienced a life-threatening capillary leak syndrome characterized by hypoxemia, ascites, pericardial effusion, pleural effusion, shock, and hepatocellular injury following G-CSF administration and peripheral blood hematopoietic progenitor cell collection [46].



# Adverse Reactions to Allogeneic Whole Blood Donation by 16- and 17-Year-Olds

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**T**HE UNREMITTING NEED AND INCREASING demand for blood components constantly challenges blood centers to maintain a safe and adequate blood supply from a decreasing pool of eligible donors that is now estimated at only 38% of the US adult population.<sup>1,2</sup> Between 2001 and 2004, the National Blood Collection and Utilization Survey documented a 0.2% decrease in whole blood and apheresis red blood cell unit collections, during a time when transfusions increased by 2%, implying a diminished reserve and a greater likelihood of episodic shortages.<sup>3</sup> In addition, the incremental restrictions imposed on donor eligibility in recent years, such as geographic deferrals for proven or perceived risk of transfusion-transmitted malaria and bovine spongiform encephalopathy, and the introduction of additional infectious disease tests, including those for Chagas disease and West Nile virus, further diminish the number of eligible blood donors and available screened blood units.<sup>4-7</sup>

In this environment, blood centers have endeavored to recruit more eligible donors by targeting appeals to underrepresented racial groups, streamlining donor history screening, eliminating unnecessary questions, obtain-

**See also Patient Page.**

**Context** Donations by minors (16- and 17-year-olds) now account for approximately 8% of the whole blood collected by the American Red Cross, but young age and first-time donation status are known to be independent risk factors for donation-related complications.

**Objective** To evaluate adverse reactions to allogeneic whole blood donation by 16- and 17-year-olds compared with older donors in American Red Cross blood centers.

**Design, Setting, and Participants** Prospective documentation of adverse events among 16- and 17-year-old donors using standardized collection protocols, definitions, and reporting methods in 2006. Data were from 9 American Red Cross blood centers that routinely collect from 16- and 17-year-olds, a population that provides 80% of its donations at high school blood drives.

**Main Outcome Measures** Rate of systemic (syncopal-type) and phlebotomy-related donor complications per 10 000 collections.

**Results** In 2006, 9 American Red Cross regions collected 145 678 whole blood donations from 16- and 17-year-olds, 113 307 from 18- and 19-year-olds, and 1 517 460 from donors aged 20 years or older. Complications were recorded in 15 632 (10.7%), 9359 (8.3%), and 42 987 (2.8%) donations in each corresponding age group. In a multivariate logistic regression model, young age had the strongest association with complications (odds ratio [OR], 3.05; 95% confidence interval [CI], 2.52-3.69;  $P < .001$ ), followed by first-time donation status (OR, 2.63; 95% CI, 2.24-3.09;  $P < .001$ ) and female sex (OR, 1.87; 95% CI, 1.62-2.16;  $P < .001$ ). Infrequent but medically relevant complications, in particular physical injury from syncope-related falls, were significantly more likely in 16- and 17-year-old donors (86 events; 5.9/10 000 collections) compared with 18- and 19-year-old donors (27 events; 2.4/10 000 collections; OR, 2.48; 95% CI, 1.61-3.82) or adults aged 20 years or older (62 events; 0.4/10 000 collections; OR, 14.46; 95% CI, 10.43-20.04). Sixteen-year-old donors who experienced even a minor complication were less likely to return to donate within 12 months than 16-year-olds who experienced uncomplicated donations (52% vs 73% return rate; OR, 0.40; 95% CI, 0.36-0.44).

**Conclusions** A higher incidence of donation-related complications and injury occurs among 16- and 17-year-old blood donors compared with older donors. The increasing dependence on recruiting and retaining young blood donors requires a committed approach to donor safety, especially at high school blood drives.

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ing variances from US Food and Drug Administration regulations to collect blood from individuals with hereditary hemochromatosis, relaxing the upper and lower age limitations for blood donation, and advocating for state legislation to collect blood from 16- and 17-year-old high school students.<sup>8-11</sup> In the American Red Cross system be-

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tween 1996 and 2005, blood collection from young donors aged 16 to 19 years increased and now accounts for 14.5% of annual donations, whereas blood donation by older individuals declined.<sup>12</sup>

Most state regulations allow blood collection from 17-year-old donors without parental consent, although 5 states maintain this requirement. At the time of this publication, 22 states or US territories allow donation by 16-year-olds with parental consent, either through adoption of legislation or the granting of variances (Alabama, Alaska, Arizona, California, Georgia, Illinois, Iowa, Kentucky, Maine, Maryland, Michigan, Minnesota, Missouri, New York, Pennsylvania, Puerto Rico, South Carolina, Tennessee, Virginia, Virgin Islands, Washington State, and Wisconsin), and 2 states allow donation by 16-year-olds without parental consent (Kansas and Oregon). California also allows donation by 15-year-olds with written permission of a parent or guardian, plus the written authorization of a physician or surgeon. The American Red Cross requires parental consent for all 16-year-old donors, does not collect from 15-year-olds, and follows state regulations or variances applicable to parental consent for collection from 17-year-old donors.

Several blood centers have demonstrated that complications, deferrals, and first-time donation rates are highest in young donors.<sup>13-19</sup> Recent escalation in blood donation by 16- and 17-year-olds prompted us to analyze data from the American Red Cross hemovigilance program regarding adverse events in 16- and 17-year-olds following allogeneic whole blood donation in 9 regional American Red Cross blood centers. These data comprise an extensive experience (> 1.5 million whole blood donations in a 12-month time frame) and provide a detailed classification of the specific complications, as well as a quantitative estimate of the uncommon but medically more serious complications of blood donation in the youngest eligible blood donors.

## METHODS

### Data Origin and Collection

The American Red Cross hemovigilance program prospectively evaluates reports of complications and injuries, including cases referred for outside medical care, after allogeneic whole blood and automated (apheresis) collection procedures in 35 blood services regions.<sup>19</sup> Collection staff in all American Red Cross regions receive standardized training, follow standard collection procedures, and use common definitions to recognize, manage, and document adverse reactions following blood collection. All major reactions that occur at the collection site and any reaction reported back to the centers are reviewed by a physician serving that center's region and tracked by the American Red Cross hemovigilance program; all cases involving outside medical care are also reviewed by the national medical director of the program.

Nine American Red Cross blood services regions were selected for this analysis because each had more than 1000 allogeneic whole blood registrations from volunteer, nonremunerated donors who were 16 years old at the time of donation between January 1, 2006, and December 31, 2006. These 9 American Red Cross blood regions collected blood in 10 states or US territories (Georgia, Illinois, Iowa, Kansas, Maryland, Missouri, New York, Oregon, Washington state, and Puerto Rico), and each region required parental permission for 16-year-old donors. High school and all other drive types (eg, church, civic organization, business) were included in the analysis.

Autologous, therapeutic, and automated collections were excluded from the analysis. Other reasons for exclusion were complications experienced by whole blood donors before phlebotomy or unrelated to phlebotomy (eg, injuries caused by other incidents at the site), or donations that were miscoded as for age, sex, or reaction category (eg, 15 citrate reactions recorded after whole blood donation).

### Classification Scheme for Donor Complications

The American Red Cross hemovigilance program classifies complications into defined categories, with severity ratings (minor or major) for certain reaction types.<sup>19</sup> Presyncopal (minor) symptoms include pallor, diaphoresis, or lightheadedness without the loss of consciousness. Short loss of consciousness (minor) is defined as lasting less than 1 minute. Long loss of consciousness (major) is defined as lasting 1 minute or more or complicated by loss of bowel or bladder control, seizures, or convulsions. Prolonged recovery is defined as presyncopal symptoms, with or without loss of consciousness, that do not resolve within 30 minutes. Small (< 25.8 cm<sup>2</sup>) and large (≥ 25.8 cm<sup>2</sup>) hematomas include bruises or infiltration and "true" hematomas with a palpable mass. Reactions classified as "other" did not otherwise fit into established reaction categories and include such reactions as hyperventilation (minor) and chest pain (major). Allergic (minor, major) reactions were recorded in the system but are not included in the analysis because of their extreme rarity (19 total reactions); only 4 allergic reactions were classified as major (eg, shortness of breath, facial edema, severe allergic symptoms) and all occurred in donors older than aged 20 years.

Complications in each category were further classified depending on whether the donor received outside medical care. Outside medical care is defined as medical advice or treatment provided by someone other than American Red Cross staff and includes emergency medical personnel responding to 911 calls, visits to a primary health care physician or specialist, or interaction with any health care professional, whether further medical attention is sought independently by the donor or at the advice of American Red Cross staff.

### Analysis of Complication and Return Donation Rates

Complication rates were calculated per 10 000 collections. The denominator includes the number of satisfactory and unsatisfactory (eg, quantity not sufficient) collections. There was a nonlinear rela-

relationship between donor age and overall rate of complications, such that reactions were disproportionately represented in donors younger than 20 years and fairly constant in age groups older than 20 years. Consequently, donor age groups were collapsed to specifically compare minor donors (16- and 17-year-olds) with young adults (18- and 19-year-olds) and adults ( $\geq 20$ -year-olds).

The effect of a reaction on the return behavior of 16-year-old donors in the 9 American Red Cross centers was evaluated in a subanalysis by comparing cohorts of 16-year-old donors who experienced either a minor or a major complication to a randomly selected control group of 16-year-old donors who experienced uncomplicated donations. Eligible donors with a minor or major reaction event and concordant control donors without a recorded reaction provided a donation between March 2005 and February 2006. Donors from each group were then followed for 365 days for a subsequent presentation event, including those that may have led to deferral.

Complication rates in donor groups stratified for age, donation status (first-time vs repeat donation to the American Red Cross), and sex were compared by calculating the 95% confidence intervals (CIs) for the proportion or by calculating odds ratios (ORs) and 95% CIs (Instat by Graphpad Inc, San Diego, California). Multivariate, stepwise logistic regression analyses were performed using SAS STAT statistical software version 8.2 (SAS Institute Inc, Cary, North Carolina). The regression analyses evaluated the independent variables (donor age, sex, donation status, drive type, region) and the dependent outcome (any complication excluding small hematoma and presyncope). A stepwise selection method was used to determine which effects entered the logistic regression model and also which effects remained in the model. A significance level of  $\leq .05$  was necessary for an effect to enter into the model and a significance level of  $\leq .05$  was necessary for an effect to remain in the model at any iteration step.

Informed consent was obtained from all donors at the time of whole blood collection, and parental permission for donation was obtained for all 16-year-old donors and for 17-year-old donors if required by state law. The American Red Cross institutional review board determined that the research satisfied criteria for exemption.<sup>20</sup>

## RESULTS

### Donations

During the study period, the 9 American Red Cross blood centers performed 44 305 and 101 373 whole blood collections from 16- and 17-year-old donors, respectively, along with 113 307 collections from 18- and 19-year-olds, and 1 517 460 from donors aged 20 years or older. As a percentage of donations, 16- and 17-year-olds provided 8.2% of donations (2.5% from 16-year-olds; 5.7% from 17-year-olds) within the 9 centers under study, and 7.5% (450 317 of 6 014 472 collections) over the entire American Red Cross system. Among the 9 centers, the contribution that 16- and 17-year-old donors made to the total collections in a region varied from 4.2% to 11.2%. The overall proportion of female donors ranged from 35% to 53%; and the overall proportion of first-time donations ranged from 12% to 29%. Eighty percent of collections from 16- and 17-year-old donors in the 9 American Red Cross regions occurred at high schools, 14% at civic/community drives, 3% at churches, and 3% at other or nonspecified drive types.

### Complications

In 2006, the 9 American Red Cross regions recorded 67 978 complications after whole blood donation in all reaction categories, for an overall rate of 382.7 per 10 000 or 3.8% of all collections. Complications occurred after 15 632 (10.7%) donations by 16- and 17-year-olds, 9359 (8.3%) by 18- and 19-year-olds, and 42 987 (2.8%) by donors aged 20 years or older. The most frequent complications in donors aged 16 and 17 years, 18 and 19 years, and 20 years and older were symptomatic

presyncope reactions (894.8, 683.1, and 198.7/10 000, respectively), and small hematomas (118.3, 105.0, 74.6/10 000, respectively; TABLE 1). The rates of loss of consciousness and major systemic (syncopal-type) complications were inversely related to donor age and more common among younger donors (FIGURE 1). Sixteen- and 17-year-olds were significantly more likely to experience any loss of consciousness and major systemic (syncopal-type) complications (53.1/10 000 collections) than 18- and 19-year-old donors (33.4 complications/10 000 collections; OR, 1.59; 95% CI, 1.41-1.80), or donors aged 20 years or older (8.0 complications/10 000 collections; OR, 6.65; 95% CI, 6.08-7.28) (Table 1). Most notably, injuries related to syncope were more common among 16- and 17-year-old donors (5.9/10 000) compared with 18- and 19-year-olds (2.4 injuries/10 000 collections; OR, 2.48; 95% CI, 1.61-3.82) or compared with donors aged 20 years or older (0.4 injuries/10 000 collections; OR, 14.46; 95% CI, 10.43-20.04) (Table 1). Excluding small hematomas, the rate of phlebotomy-related complications was not different among 16- and 17-year-olds (4.4/10 000) compared with 18- and 19-year-olds (2.9 complications/10 000 collections; OR, 1.51; 95% CI, 0.99-2.30) but was statistically significant compared with donors aged 20 years or older (1.5 complications/10 000 collections; OR, 2.87; 95% CI, 2.18-3.79) (Table 1).

A secondary analysis of donation-related complications compared 16-year-olds to 17-year-olds. The rate of presyncopal reactions was statistically but only marginally higher in 16-year-olds (961.5/10 000) compared with 17-year-olds (865.6 reactions/10 000 collections; OR, 1.12; 95% CI, 1.08-1.17). Among first-time donations, 16-year-olds had statistically higher presyncopal complication rates than 17-year-olds (1015 vs 971/10 000; OR, 1.05; 95% CI, 1.01-1.10). Differences between 16- and 17-year-olds in the other reaction categories did not reach statistical significance (data not shown).

**Table 1.** Complication Rates of Allogeneic Whole Blood Donation

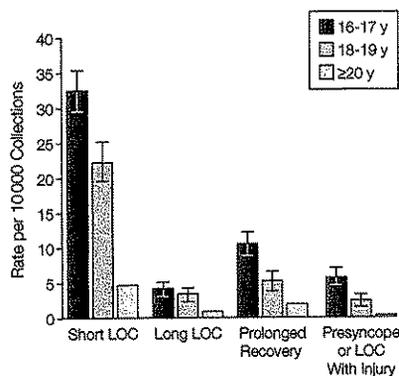
Complication	No. of Donor Complication Events (Rate per 10 000 Collections), by Donor Age, y			OR (95% CI), by Donor Age, y	
	16-17	18-19	≥20	16-17 vs 18-19	16-17 vs ≥20
No. of donations	145 678	113 307	1 517 460		
Systemic (syncopal-type)					
Presyncope	13 035 (894.8)	7 740 (683.1)	30 151 (198.7)	1.34 (1.30-1.38)	4.85 (4.75-4.95)
Short LOC <sup>a</sup>	473 (32.5)	253 (22.3)	713 (4.7)	1.46 (1.25-1.70)	6.93 (6.17-7.78)
Long LOC (major) <sup>a</sup>	61 (4.2)	39 (3.4)	154 (1.0)	1.22 (0.81-1.82)	4.13 (3.07-5.55)
Prolonged recovery (major) <sup>a</sup>	154 (10.6)	60 (5.3)	289 (1.9)	2.00 (1.48-2.69)	5.56 (4.57-6.76)
Presyncope or LOC with injury (major) <sup>a</sup>	86 (5.9)	27 (2.4)	62 (0.4)	2.48 (1.61-3.82)	14.46 (10.43-20.04)
Subtotal, excluding presyncope	774 (53.1)	379 (33.4)	1 218 (8.0)	1.59 (1.41-1.80)	6.65 (6.08-7.28)
Phlebotomy-related complications					
Small hematoma <sup>a</sup>	1 724 (118.3)	1 190 (105.0)	11 327 (74.6)	1.13 (1.05-1.22)	1.59 (1.51-1.68)
Large hematoma (major) <sup>a</sup>	16 (1.1)	9 (0.8)	44 (0.3)	1.38 (0.61-3.13)	3.79 (2.14-6.71)
Nerve irritation (major) <sup>a</sup>	20 (1.4)	8 (0.7)	77 (0.5)	1.94 (0.86-4.42)	2.71 (1.65-4.43)
Arterial puncture (major) <sup>a</sup>	28 (1.9)	16 (1.4)	111 (0.7)	1.36 (0.74-2.52)	2.63 (1.74-3.98)
Subtotal, excluding small hematoma	64 (4.4)	33 (2.9)	232 (1.5)	1.51 (0.99-2.30)	2.87 (2.18-3.79)
Other (major, minor) <sup>a,b</sup>	35 (2.4)	17 (1.5)	59 (0.4)	1.60 (0.90-2.86)	6.18 (4.07-9.39)
Overall	15 632 (1073.1)	9 359 (826.0)	42 987 (283.3)	1.34 (1.30-1.37)	4.12 (4.04-4.20)

Abbreviations: CI, confidence interval; LOC, loss of consciousness; OR, odds ratio.

<sup>a</sup>See "Classification Scheme for Donor Complications" section for descriptions of complications.

<sup>b</sup>Other includes reactions that do not fit into other categories. Allergic reactions were not included in the analysis because of their rarity (19 total; 3, 1 and 15 in 16-17-y-olds, 18-19-y-olds, ≥20 years, respectively).

**Figure 1.** Complication Rates of Loss of Consciousness and Major Systemic (Syncopal-Type) Complications by Donor Age



LOC indicates loss of consciousness. The rate of LOC, prolonged recovery, and syncope-related injury as a function of donor age is shown with error bars denoting 95% confidence intervals. Variability was plotted for donors aged 20 years or older but error bars for 95% confidence intervals are very small (the rate for short LOC: 4.7 [95% CI, 4.4-5.0]; for long LOC: 1.0 [95% CI, 0.9-1.2]; for prolonged recovery: 1.9 [95% CI, 1.7-2.1]; and for presyncope or LOC with injury: 0.4 [95% CI, 0.3-0.5]).

A stratified analysis evaluated the systemic (syncopal-type) complication rates in comparable donor subgroups with respect to age, donation status, and sex.

Within each corresponding donor subgroup, the complication rate was inversely related to donor age when sorted for donation status and sex (FIGURE 2). Among first-time donations by female donors, the rate of systemic (syncopal-type) complications in 16- and 17-year-olds (1214/10 000) was significantly higher compared with the corresponding subgroup of 18- and 19-year-olds (1004 complications/10 000 collections; OR, 1.24; 95% CI, 1.18-1.30) or donors aged 20 years or older (689 complications/10 000 collections; OR, 1.87; 95% CI, 1.80-1.94) (TABLE 2). Similarly, the highest systemic (syncopal-type) reaction rate was observed in the youngest donor group (16- and 17-year-olds) in each donor stratum (female/repeat donors, male/first-time donors, and male/repeat donors) (Figure 2).

In a stepwise logistic regression analysis of correlates of complications (loss of consciousness and major systemic [syncopal-type] plus major phlebotomy-related complications), young age demonstrated the strongest association (OR, 3.05; 95% CI, 2.52-3.69;  $P < .001$ ), followed by first-time donation status (OR, 2.63; 95% CI, 2.24-3.09;  $P < .001$ ), and female sex (OR, 1.87; 95% CI, 1.62-

2.16;  $P < .001$ ) (TABLE 3). There were significant but lesser effects in reaction rates when smaller regions were compared with the largest one (Table 3). The drive type (high school drives compared with other drive types, eg, church, civic) was not significantly associated with donor complications in the multivariate analysis.

#### Requirement for Outside Medical Care After Blood Donation

Among all donors, 583 were referred by collection staff or reported as receiving outside medical care for adverse events related to whole blood donation in 2006, for an overall rate of 3.3 per 10 000 donations. Eighty-five 16- and 17-year-olds (5.8 individuals/10 000 donations) received outside medical care, which was significantly more frequent than the rate observed in adults aged 20 years or older (433 events; 2.9 individuals/10 000 donations; OR, 2.05; 95% CI, 1.62-2.58) but not different from that observed for 18- and 19-year-old donors (65 events; 5.7 individuals/10 000 donations; OR, 1.02; 95% CI, 0.74-1.40) (TABLE 4). Among 16- and 17-year-olds, systemic (syncopal-type) complications accounted for 66% of cases of

outside medical care, and phlebotomy-related complications accounted for the remainder. The most common reason for outside medical care was syncope-related injury, especially in donors aged 16 to 19 years. Thirty-two 16- and 17-year-old donors received outside medical care after syncope-related falls: 25 with head injuries (eg, concussion, contusion, laceration); 3 with facial lacerations requiring sutures; 3 with dental injuries; and 1 with a broken jaw. Twenty-two of 32 injured donors (69%) who received outside medical care weighed 59 kg or more; only 4 of 32 (12.5%) weighed less than 54 kg. The injuries to young donors usually occurred soon after donation in the canteen area (17 events; 53%); in the restroom (5 events; 16%); or in another area of the school (9 events; 28%); and 1 event occurred outside the school (3%).

**Return Behavior**

Fifty-two percent (1861 of 3559) of 16-year-old donors who experienced a minor complication returned to donate in the next year compared with 73% (2613 of 3559) who had an uncomplicated donation (OR, 0.40; 95% CI, 0.36-0.44). Return donation was even less likely among 16-year-old donors if they experienced a major complication (31%; 30 of 98) compared with the no complication group (81%; 79 of 98; OR, 0.11; 95% CI, 0.05-0.21) (TABLE 5).

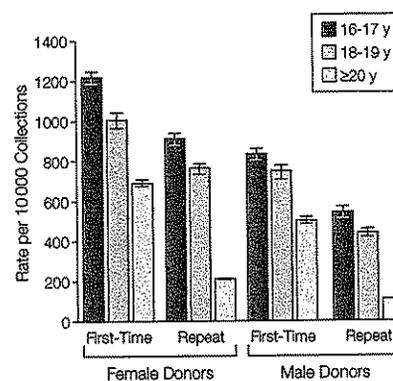
**COMMENT**

Blood centers have a dual responsibility to provide an adequate supply of blood components to the communities they serve and to protect the safety of their volunteer donors. With the increasing collection of whole blood from minors aged 16 and 17 years in recent years, we sought to describe and quantify the adverse reactions experienced by these donors compared with 18- and 19-year-olds, and compared with adults aged 20 years and older. This analysis demonstrates that most donors in all age groups had uncomplicated donations, but young age had the strongest association with complications followed by first-time donation status and female sex; there was also some variation between regional blood centers.

The most common systemic and phlebotomy-related complications of blood donation (ie, presyncope, small hematoma), although uncomfortable for the donor, are medically inconsequential. The significance of these minor complications, however, lies primarily in the observation that any complication, even a minor one, reduces the likelihood of return donation, as does any temporary deferral for other reasons.<sup>21</sup> In addition, minor complications may be an indirect measure of more serious complications, although this is difficult to assess because of infrequent occurrence. Although the absolute differences in

complication rates between the age groups are relatively small in this study, they are statistically significant and remain a potential medical concern: the risk of syncope-related injury was 2.5 times more likely in 16- and 17-year-old donors (5.9/10 000) compared with 18- and 19-year-olds (2.4 injuries/10 000 donations), and 14 times more likely compared with donors aged 20 years or older (0.4 injuries/10 000 do-

**Figure 2.** Total Systemic (Syncope-Type) Complication Rates by Age, Sex, and Donation Status



The rate of presyncope and systemic (syncope-type) complications in stratified donor subgroups with respect to age, sex, and donation status are shown with error bars denoting 95% confidence intervals. Variability was plotted for donors aged 20 years or older but error bars for 95% confidence intervals are very small (the rate for repeat females: 214 [95% CI, 210-217]; and for repeat males: 106 [95% CI, 104-108]).

**Table 2.** Total Systemic (Syncope-Type) Complication Rates by Donor Age, Sex, and Donation Status<sup>a</sup>

Donor Sex and Donation Status	16-17 y			18-19 y			≥20 y			OR (95% CI)	
	No. of Events	No. of Donations	Rate/10 000 Collections (95% CI)	No. of Events	No. of Donations	Rate/10 000 Collections (95% CI)	No. of Events	No. of Donations	Rate/10 000 Collections (95% CI)	16-17 y vs 18-19 y	16-17 y vs ≥20 y
Female											
First-time	6512	53 627	1214 (1187-1242)	2220	22 121	1004 (964-1043)	6331	91 830	689 (673-706)	1.24 (1.18-1.30)	1.87 (1.80-1.94)
Repeat	2767	30 458	909 (876-941)	3053	40 156	760 (734-786)	13 340	624 358	214 (210-217)	1.21 (1.15-1.28)	4.58 (4.39-4.78)
Male											
First-time	3412	41 020	832 (805-859)	1486	19 986	744 (707-780)	4070	80 741	504 (489-519)	1.13 (1.06-1.20)	1.71 (1.63-1.79)
Repeat	1118	20 573	543 (513-574)	1360	31 044	438 (415-461)	7627	720 521	106 (104-108)	1.25 (1.16-1.36)	5.37 (5.04-5.73)
Total	13 809	145 678	948 (933-963)	8119	113 307	717 (702-732)	31 368 <sup>b</sup>	1 517 450 <sup>b</sup>	207 (205-209)	1.36 (1.32-1.40)	4.96 (4.86-5.07)

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Total systemic (syncope-type) complications include presyncope, short loss of consciousness, long loss of consciousness, loss of consciousness with injury, and prolonged recovery.

<sup>b</sup>The total does include 6 first-time donations, 4 repeat donations, and 1 event of faint reaction for which donor sex was not reported.

nations). Almost half of all injuries recorded by the collection staff in the 9 American Red Cross regions occurred in 16- and 17-year-old donors; and many (eg, concussion, laceration requiring stitches, dental injuries, broken jaw) were severe enough to require outside medical care. Finally, there is a strong correlation between even minor com-

plications and the failure to return to donate blood again among 16-year-olds. Consequently, any negative experience diminishes the likelihood of return blood donation, and increases the possibility that a short-term yield in donations incurs the ultimate expense of deterring future blood donation by young donors.

These findings are particularly pertinent at a time when blood centers are becoming increasingly reliant on young donors to maintain an adequate blood supply. Zou et al describe increasing recruitment of first-time donors in the 16- to 19-year-old age groups and declining rates of blood donation in older age groups.<sup>12</sup> The pressing need to expand the donor pool raises the inherent dilemma of putting minor-age donors at any degree of risk and the difficulty in defining a level of risk that may be reasonably tolerated. The recruitment of minors for blood donation provides a measurable benefit to the national blood supply in terms of both safety and availability. Young donors have lower prevalence and incidence of transfusion-transmitted infectious diseases compared with older donors,<sup>22</sup> and 16- and 17-year-old donors contribute a significant proportion (approximately 8%) of the units

collected by the American Red Cross. If the practice of collecting blood from 16-year-olds was extended nationwide, others have estimated that an additional 200 000 additional units could be added to the nearly 15 million units collected annually in the United States.<sup>11</sup>

Complication rates after allogeneic whole blood donation are known to be higher in young and first-time donors, and our results confirm and extend these observations to the youngest eligible donor group.<sup>13-19</sup> The mechanisms responsible for the increased susceptibility to systemic (syncopal-type) complications following blood donation in young donors, however, are not clearly defined. Central thalamic pathways and peripheral and ventricular baroreceptor sensitivity may play a central role, and the age-dependent differences in responses to physical and emotional stress may underlie the observed differences in young donors compared with older donors.<sup>23,24</sup> A psychological component to the propensity for reactions among young anxious donors has also been described, and the phenomenon of "epidemic fainting" or clusters of reactions among donors who witness a reaction at a blood drive is widely recognized although poorly studied.<sup>25</sup> In the cur-

**Table 3.** Multivariate Logistic Regression Model of Correlates of Systemic (Syncopal-Type) and Major Phlebotomy-Related Donation Complications

Risk Factor	Odds Ratio (95% Wald Confidence Limits)	P Value
Age group, y		
≥ 20	1.00 [Reference]	
16-17	3.05 (2.52-3.69)	<.001
18-19	2.55 (2.13-3.05)	<.001
Donation status		
Repeat	1.00 [Reference]	
First-time	2.63 (2.24-3.09)	<.001
Sex		
Male	1.00 [Reference]	
Female	1.87 (1.62-2.16)	<.001
Region in order of decreasing size <sup>a</sup>		
A	1.00 [Reference]	
B	0.72 (0.57-0.90)	.03
C	0.65 (0.49-0.85)	.009
D	0.46 (0.35-0.61)	<.001
E	1.41 (1.13-1.75)	<.001
F	0.95 (0.72-1.26)	.37
G	0.90 (0.66-1.22)	.75
H	1.82 (1.41-2.34)	<.001
I	0.56 (0.37-0.84)	.01

<sup>a</sup>Total collections range from 294 828 in region A to 77 646 in region I.

**Table 4.** Outside Medical Care

Complications	No. of Donor Complication Events Needing Outside Medical Care (Rate per 10 000 Collections) [95% CI], by Age, y			OR (95% CI), by Donor Age, y	
	16-17	18-19	≥20	16-17 vs 18-19	16-17 vs ≥20
No. of donations	145 678	113 307	1 517 460		
Systemic (syncopal-type) complications					
Presyncope	0	1 (0.1) [0.0-0.3]	4 (0) [0]		
Short LOC <sup>a</sup>	2 (0.1) [0.0-0.3]	3 (0.3) [0.0-0.6]	8 (0.05) [0.0-0.1]	0.52 (0.09-3.10)	2.60 (0.55-12.26)
Long LOC <sup>a</sup>	6 (0.4) [0.1-0.7]	6 (0.5) [0.1-1.0]	43 (0.3) [0.2-0.4]	0.78 (0.25-2.41)	1.45 (0.62-3.41)
Prolonged recovery	16 (1.1) [0.6-1.6]	12 (1.1) [0.5-1.7]	100 (0.7) [0.5-0.8]	1.04 (0.49-2.19)	1.67 (0.98-2.83)
Presyncope or LOC with injury	32 (2.2) [1.4-3.0]	15 (1.3) [0.7-2.0]	38 (0.3) [0.2-0.3]	1.66 (0.90-3.06)	8.77 (5.48-14.04)
Phlebotomy-related complications					
Small hematoma <sup>a</sup>	1 (0.1) [0.0-0.02]	2 (0.2) [0.0-0.4]	9 (0.1) [0.0-0.1]	0.39 (0.04-4.29)	1.16 (0.15-9.14)
Large hematoma <sup>a</sup>	13 (0.9) [0.4-1.4]	8 (0.7) [0.2-1.2]	95 (0.6) [0.5-0.8]	1.26 (0.52-3.05)	1.43 (0.80-2.55)
Nerve irritation	4 (0.3) [0.0-0.5]	5 (0.4) [0.1-0.8]	57 (0.4) [0.3-0.5]	0.62 (0.17-2.32)	0.73 (0.27-2.01)
Arterial puncture	5 (0.3) [0.0-0.6]	2 (0.2) [0.0-0.4]	16 (0.1) [0.1-0.2]	1.94 (0.38-10.02)	3.26 (1.19-8.89)
Other	6 (0.4) [0.1-0.7]	11 (1.0) [0.4-1.5]	63 (0.4) [0.3-0.5] <sup>b</sup>	0.42 (0.16-1.15)	0.99 (0.43-2.29)
Total, all categories of outside medical care	85 (5.8) [4.6-7.1]	65 (5.7) [4.5-7.3]	433 (2.9) [2.7-3.2]	1.02 (0.74-1.40)	2.05 (1.62-2.58)

Abbreviations: CI, confidence interval; LOC, loss of consciousness; OR, odds ratio.

<sup>a</sup>See "Classification Scheme for Donor Complications" section for descriptions of complications.

<sup>b</sup>Includes 6 allergic reactions.

**Table 5.** Effect of Complications on Return Rates of Blood Donation Among 16-Year-Old Donors

	Minor Complication <sup>a</sup>	No Complication	OR (95% CI)	Major Complication <sup>a</sup>	No Complication	OR (95% CI)
Returned, No. (%)	1861 (52)	2613 (73)		30 (31)	79 (81)	
Did not return, No. (%)	1698 (48)	946 (27)		68 (69)	19 (19)	
Total donors	3559	3559	0.40 (0.36-0.44)	98	98	0.11 (0.05-0.21)

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>See "Classification Scheme for Donor Complications" section for descriptions of complications.

rent analysis, however, drive setting (high school vs other) was not an independent predictor of complications, which suggests that the drive environment does not contribute to the differences observed between age groups.

We recognize the limitations of the current analysis, which did not evaluate the relative contribution of some previously described donor characteristics to the risk of complications after whole blood donation, such as low weight or white race.<sup>8,17,18,26,27</sup> However, our data show that low-weight donors (<59 kg) are not overrepresented in the cohort of more serious donation-related complications that received outside medical care. Another potential limitation is that the cases associated with outside medical care may be subject to reporting or treatment bias among 16- and 17-year-olds if their parents are more likely to be involved in the decision to seek medical assistance or if collection staff are more attentive to young donors. The increased occurrence of minor phlebotomy-related complications (eg, small hematomas) in the youngest donors suggests that reporting bias may exist because there is no physiologic basis or expectation that hematomas or bruises are more likely to occur in healthy 16- and 17-year-old donors compared with adults. Suspected arterial puncture, however, demonstrated a more significant increase among young (16- to 19-year-old) donors compared with adults, and has been previously postulated to reflect predisposing anatomical conditions in the younger donors.<sup>28,29</sup> While we cannot control for increased staff or parental attention and possible reporting bias on high school drives, we have no evidence that collection staff are

more likely to report syncope-related injuries on high school drives than on other drive types.

Other blood centers use different classification schemes and have reported similar trends in the rates of mild, moderate, and severe complications among young donors.<sup>13-18,30</sup> Direct comparison of blood centers, however, is not possible because of subjective differences in defining, recognizing, and reporting donor complications, as well as possible differences in donor demographics that contribute to variation in complication rates. Even within the American Red Cross, variability was seen in the reported donor complication rates among the 9 American Red Cross regions, and those that collected from more donors generally had lower complication rates than the smaller regions. We have not identified correlates of lower complication rates related to different practices among the regions, and these differences may instead be related to donor demographics and any combination of staff experience, attention, or reporting bias and are the focus of further study.

Several interventions (eg, having the donor drink 16 oz water shortly before donation, or using applied muscle tension, distraction, or behavior modification) have been demonstrated to marginally reduce donor complication rates,<sup>31-33</sup> but no single measure has been shown to prevent a majority of systemic reactions or to prevent the rare but more serious complications, such as syncope-related injury after whole blood donation. Reducing the relative proportion of blood loss by requiring a higher donor weight or by reducing the collection volume have also been proposed as safety measures. How-

ever, we show that over two-thirds (69%) of the injuries that required outside medical care in this cohort occurred in donors weighing more than 59 kg, and others have presented data suggesting that a switch to a larger collection set (500 mL vs 450 mL) had no effect on complication rates.<sup>34,35</sup> Consequently, these data suggest that increasing the weight requirement or decreasing the collection volume would have marginal benefit, limited to a small subset of donors, and would have little effect on the incidence of more serious complications. Alternatively, the possibility that automated collection procedures with concurrent intravascular fluid replacement may reduce the incidence of severe complications is being further explored.

### Conclusions

The current analysis demonstrates a significantly increased risk of minor and major complications of allogeneic whole blood donation by 16- and 17-year-old individuals compared with older donors that extends to an increased risk of syncope-related physical injury and complications requiring outside medical care. Although the absolute magnitudes of the differences between the age groups are relatively small, the differences are statistically significant; young age is the strongest correlate of major complications and 16- and 17-year-old donors accounted for almost half of the syncope-related injuries in this series.

These data on common and infrequent complications of blood donation should be considered when age limits are deliberated by state authorities. The relatively comparable reaction rates in 16- and 17-year-old donors, and their increased complication

rates compared with young adults and adults, suggest the need for a consistent approach. Blood centers have an obligation to constantly monitor risks of blood donation and to make a concerted and committed effort to achieve the lowest possible rate of complications. Although zero risk may not be attainable even in adults, the rate of complications in minors calls for ongoing attention to a sustained operational effort that is continually focused on donation safety.

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**Study concept and design:** Eder, Benjamin.

**Acquisition of data:** Eder, Dy, Notari, Benjamin.

**Analysis and interpretation of data:** Eder, Hillyer, Dy, Notari, Benjamin.

**Drafting of the manuscript:** Eder, Hillyer, Benjamin.

**Critical revision of the manuscript for important intellectual content:** Eder, Hillyer, Dy, Notari.

**Statistical analysis:** Eder, Dy, Notari.

**Administrative, technical, or material support:** Benjamin.

**Study supervision:** Hillyer, Benjamin.

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## REFERENCES

- Riley W, Schwei M, McCullough J. The United States' potential blood donor pool: the prevalence of donor-exclusion factors on the pool of potential donors. *Transfusion*. 2007;47(7):1180-1188.
- Sullivan MT, Cotten R, Read EJ, Wallace EL. Blood collection and transfusion in the United States in 2001. *Transfusion*. 2007;47(3):385-394.
- Whitaker BJ, Sullivan M; US Department of Health and Human Services. *The 2005 Nationwide Blood Collection and Utilization Survey Report*. <http://www.hhs.gov/bloodsafety/2005NBCUS.pdf>. Accessed February 14, 2008.
- Leiby DA. Making sense of malaria. *Transfusion*. 2007;47(9):1573-1577.
- O'Brien SF, Chiavetta JA, Goldman M, et al. Predictive ability of sequential surveys in determining donor loss from increasingly stringent variant Creutzfeldt-Jakob disease deferral policies. *Transfusion*. 2006;46(3):461-468.
- Busch MP, Wright DJ, Custer B, et al. West Nile virus infections projected from blood donor screening data, United States, 2003. *Emerg Infect Dis*. 2006;12(3):395-402.
- Centers for Disease Control and Prevention. Blood donor screening for Chagas disease—United States, 2006-2007. *Morb Mortal Wkly Rep*. 2007;56(7):141-143. <http://www.cdc.gov/mmwr/PDF/mmwrhtml/mm5607a2.htm>. Accessed September 14, 2007.
- Tomasulo PA, Anderson AJ, Paluso MB, et al. A study of criteria for blood donor deferral. *Transfusion*. 1980;20(5):511-518.
- Kamel HT, Bassett MB, Custer B, et al. Safety and donor acceptance of an abbreviated donor history questionnaire. *Transfusion*. 2006;46(10):1745-1753.
- Shehata N, Kusano R, Hannach B, Hume H. Reaction rates in allogeneic donors. *Transfus Med*. 2004;14(5):327-333.
- Davey RJ. Recruiting blood donors: challenges and opportunities. *Transfusion*. 2004;44(4):597-600.
- Zou S, Musavi F, Notari EP IV, Fang CT; ARC-NET Study Group. Changing age distribution of the blood donor population in the US. *Transfusion*. 2008;48(2):251-257.
- Harkin R, Lessig M. Reaction incidence among teen-aged first-time and repeat whole blood and apheresis donors [abstract] in: abstracts of the AABB annual meeting, October 20-23, 2007, Anaheim, California. *Transfusion*. 2007;47(3 suppl):105A.
- Gammon RR, Malone J, Gatto J, Newberg NR. Implementation of a 16 year-old donor program: our experience [abstract] in: abstracts from the AABB annual meeting, Miami Beach, Florida, October 21-24, 2006. *Transfusion*. 2006;46(9 suppl):82A.
- Nguyen KT, Hirschler NV. Adverse donor reactions in high school aged donors [abstract] in: abstracts of the AABB annual meeting, October 20-23, 2007, Anaheim, California. *Transfusion*. 2007;47(3 suppl):107A.
- Newman BH. Blood donor complications after whole-blood donation. *Curr Opin Hematol*. 2004;11(5):339-345.
- Trouern-Trend JJ, Cable RG, Badon SJ, Newman BH, Popovsky MA. A case-controlled multicenter study of vasovagal reactions in blood donors: influence of sex, age, donation status, weight, blood pressure, and pulse. *Transfusion*. 1999;39(3):316-320.
- Newman BH, Satz SL, Janowicz NM, Siegfried BA. Donor reactions in high-school donors: the effects of sex, weight, and collection volume. *Transfusion*. 2006;46(2):284-288.
- Eder AF, Dy BA, Kennedy JA, Notari EP, et al. The American Red Cross Donor Hemovigilance Program, complications of donation reported in 2006. *Transfusion*. In press.
- US Department of Health and Human Services. 45 CFR 46. Public welfare protection of human subjects. <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116>. Accessed April 24, 2008.
- Custer B, Chinn A, Hirschler NV, Busch MP, Murphy EL. The consequences of temporary deferral on future whole blood donation. *Transfusion*. 2007;47(8):1514-1523.
- Watanabe KK, Williams AE, Schreiber GB, Ownby HE; Retrovirus Epidemiology Donor Study. Infectious disease markers in young blood donors. *Transfusion*. 2000;40(8):954-960.
- Maisel WH, Stevenson WG. Syncope-getting to the heart of the matter. *N Engl J Med*. 2002;347(12):931-933.
- Gribbin B, Pickering TG, Sleight P, Peto R. Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res*. 1971;29(4):424-431.
- Boynton MH, Taylor ES. Complications arising in donors in a mass blood procurement project. *Am J Med Sci*. 1945;209:421-436.
- Newman BH, Siegfried BA, Buchanan LA. Donor reactions among African-American and Caucasian first-time whole blood donors (Letter). *Transfusion*. 2005;45(8):1398-1399.
- Szelei-Stevens K, Szazama K. Reactions to blood donation in Caucasian teenagers. *Transfusion*. 2006;46(11):2030-2031.
- Rader AW, Kish K, Chambers LA, Wissel ME. Arterial punctures during phlebotomy are more likely in young and male donors [abstract] in: abstracts of the AABB, 58th annual meeting, October 15-18, 2005, Seattle, Washington. *Transfusion*. 2005;45(3 suppl):88A. doi:10.1111/j.1537-2995.2005.00629.1.x.
- Newman BH. Arterial puncture phlebotomy in whole-blood donors. *Transfusion*. 2001;41(11):1390-1392.
- Wiltbank TB, Giordano GF. The safety profile of automated collections: an analysis of more than 1 million collections. *Transfusion*. 2007;47(6):1002-1005.
- Newman B, Tommolino E, Andreozzi C, Joychan S, Pocedic J, Heringhausen J. The effect of a 473-mL (16 oz) water drink on vasovagal donor reaction rates in high-school students. *Transfusion*. 2007;47(8):1524-1533.
- Ditto B, France CR, Lavoie P, Roussos M, Adler SJ. Reducing reactions to blood donation with applied muscle tension: a randomized controlled trial. *Transfusion*. 2003;43(9):1269-1275.
- Bonk VA, France CR, Taylor BK. Distraction reduces self-reported physiological reactions to blood donation in novice donors with a blunting coping style. *Psychosom Med*. 2001;63(3):447-452.
- Kakalya RM, Burns S, Dausch D. Comparison of systemic reactions among blood donors with 450 mL and 500 mL whole blood donation [abstract] in: abstracts of papers to be presented at the AABB, 58th annual meeting, October 15-18, 2005, Seattle, Washington. *Transfusion*. 2005;45(3 suppl):88A. doi:10.1111/j.1537-2995.2005.00629.1.x.
- Bianco C, Robins JL. Whole blood collection volumes and donor safety: equivalence between 450 mL and 500 mL collection sets [abstract] in: 47th annual meeting of the American Association of Blood Banks, San Diego, California, November 12-17, 1994. *Transfusion*. 1994;34(11 suppl):15S.