It is time to reconsider the risks of transfusing RhD negative females of childbearing potential with RhD positive red blood cells in bleeding emergencies

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Conventional teaching and practice indicates that females of childbearing potential (FCP) whose RhD (D) type is either unknown or who are D- should receive D- cellular blood products. This concept was reinforced in a recent AABB bulletin on group O red blood cells (RBCs) and their use in massive bleeding situations.[1] The concern has been that a D- FCP who is exposed to D+ RBCs in an RBC, whole blood, or platelet unit could become alloimmunized to the D antigen with the potential for loss of a future D+ fetus through hemolytic disease of the fetus and newborn (HDFN). Alloimmunization to other RBC antigens like K and c can also result in HDFN, but these antigens are not as immunogenic as D. Thus, this commentary will focus on D alloimmunization. The concern of transfusing D- FCPs with D+ RBCs has persisted even as major advances have been made in pre-hospital resuscitation and in the care of fetuses being carried by alloimmunized mothers. This commentary will describe the historical and contemporary outcomes of HDFN and present the modern-day risks of alloimmunization and adverse fetal outcomes, including death, caused by these antibodies weighed against the growing evidence demonstrating the importance of early transfusions in traumatically injured and massively bleeding patients. The aim of this commentary is to help inform RBC resuscitation strategies and risk assessments for massively bleeding FCPs who are either D- or D type unknown. This commentary discusses FCPs in general; for the purpose of institutional policies, the exact age range of a FCP, both on the lower and upper ends, should be defined locally.

HISTORY OF HDFN AND ITS EARLY AND CURRENT MANAGEMENT

The natural history of HDFN is that of progressive fetal anemia mediated by the transplacental passage of maternal IgG RBC antibodies, stimulated primarily by previous pregnancies,[2] that bind to and promote the destruction of fetal RBCs. Severe fetal anemia initiates a pathophysiologic cascade that ultimately leads to third-spacing of fluid in various body compartments, a condition known as erythroblastosis fetalis (also known as hydrops fetalis). Before the era of fetal medicine in the 1980s, management options included preterm delivery or an attempt at intrauterine transfusion (IUT). The former was complicated by problems of prematurity in an already hyperbilirubinemic, hydropic fetus. The latter was compromised by lack of fetal intravascular access, necessitating intraperitoneal transfusion. The perinatal mortality rate from HDFN was distressingly high (50%) as was the morbidity of survivors.[3] The advent of high-resolution ultrasound fundamentally changed both the diagnosis and management of HDFN. Noninvasive diagnosis of fetal anemia by ultrasound assessment of middle cerebral artery peak systolic velocity (MCA-PSV) replaced repeated amniocentesis, which was known to both rupture membranes and accelerate the

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disease from repeated fetal-maternal hemorrhage.[4] Ultrasound also allowed for easier and safer access to the fetal intravascular compartment through cordocentesis, which in turn allowed for accurate assessment of fetal anemia, and for IUT. The combination of the early detection of severe fetal anemia before hydrops fetalis develops, and safe IUT have virtually eliminated the progression of RBC alloimmunization to severe HDFN-mediated erythroblastosis fetalis in developed countries.[5] Intrauterine transfusions themselves coupled with more effective intensive phototherapy and the use of intravenous immune globulin (IVIG) in affected neonates have reduced the need for exchange transfusion postnatally.[6,7] Late onset anemia in affected neonates is still a concern but with close monitoring can be identified and treated successfully.[8]

MODERN EMERGENCY RESUSCITATION STRATEGIES FOR MASSIVELY BLEEDING PATIENTS

It is known that crystalloid fluid resuscitation should not be the mainstay of trauma resuscitation.[9] The evidence for the benefits of transfusing blood products to massively bleeding civilian and military patients as close to the time of injury as possible is accumulating. The multicenter Prehospital Air Medical Plasma (PAMPER) randomized trial revealed that 30-day mortality was improved amongst those who received plasma during their helicopter medical evacuation compared to patients who received the pre-hospital standard of care, which in many cases was crystalloid fluid only.[10] In a secondary analysis of this trial, the greatest survival benefit was demonstrated amongst those who received both RBCs and plasma together compared to those who received RBCs or plasma alone. In this analysis, receipt of any blood product during the helicopter evacuation produced a significantly improved 30-day survival rate compared to patients who received crystalloids alone.[11] Furthermore, a secondary analysis of the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial that compared outcomes of trauma patients who were resuscitated with two different blood product ratios found a 5% increase in mortality for every minute that blood products were not provided to a trauma patient after the massive transfusion protocol (MTP) had been activated.[12] Lastly, two recent studies of military casualties revealed that the prompt transfusion of blood products resulted in impressive reductions in mortality.[13,14] These findings underscore the importance of having blood products available early in the resuscitation of massively bleeding trauma patients.

D POSITIVE OR D NEGATIVE? WHAT'S THE RISK?

If D- RBCs were in ample supply, it would be simple to supply helicopters, ambulances, and in-hospital refrigerators that contain uncrossmatched RBCs with group O- RBCs. Nobody would have to think twice about what kind of RBCs to supply to a massively bleeding 24-year-old female trauma patient who has just taken her 19th group O- RBC unit and the operating room is asking for yet another round of the MTP, or what should be the D type of uncrossmatched RBCs to stock in the emergency room.[15] Only approximately 10% of RBC collections around the world are group O-,[16] while demand for O- RBCs is much higher.[17] Thus, O- RBCs are a resource that needs to be carefully managed, and they are generally not carried by pre-hospital emergency service providers in the US although they are carried by emergency responders in some other western countries.[18] So for whom are we saving these uncommon units? Primarily for D- FCPs and children. The question is not, should we provide D- RBCs to D- FCPs when their needs can be met with a few RBC units from the available inventory at the hospital blood bank during elective surgery? The more difficult question is what should we do when faced with a massively bleeding D- or D type unknown FCP who needs blood unexpectedly or early in her resuscitation and/or who will require a large quantity of RBCs, especially in the pre-hospital setting where early transfusion portends a survival advantage? As all AABB accredited hospitals need to have a policy for when to switch bleeding D- or D type unknown FCPs to D+ RBCs,[19] the essential question to answer is what are the current risks associated with D alloimmunization in FCPs?

The risk assessment process requires the identification of the hazard, and then an assessment of the risk in proportion to the hazard. The modern-day probability of a D- FCP exposed to D+ blood products becoming alloimmunized to the D antigen and then experiencing either fetal death or significant developmental neurological morbidity in the child because of this anti-D antibody is calculated to be approximately 0.3%. The following sections explain how this probability figure was derived by answering these five risk analysis questions:

1. What is the rate of survival in trauma with severe bleeding?

Answer: approximately 76%.

This is a complicated question to answer, as survival after trauma depends on many factors. The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) study was a large study of transfusion practices in severely bleeding trauma patients and it demonstrated an overall rate of 30-day mortality of about 24%.[20] Of the 164 patients who died within 30 days in that study, 86/164 (52%) died of exsanguination.

2. What is the rate of D alloimmunization amongst hospitalized D- recipients of at least one D+ RBC?

Answer: approximately 21%.

The conventional teaching is that there is an approximately 80% D alloimmunization rate amongst D- recipients of D+ RBCs. This figure is factually accurate, however it is derived from studies of *healthy* D- volunteers who received D+ RBCs 40-50 years ago.[21–23] In today's era of patient blood management and evidence-based transfusion decisions,

healthy people are rarely transfused with RBCs. Thus, it is important to consider the rate of D alloimmunization in *sick*, hospitalized patients who receive at least one unit of D+ RBCs. Three retrospective studies in this population have found uncorrected D alloimmunization rates after receiving a D+ RBC transfusion of 20.5%,[24] 21.4%,[25] and 22.4%.[26] Combining the number of patients who became D alloimmunized and dividing it by the total number of D- recipients in these three studies gives a D alloimmunization rate of 20.5% (72/351, 95% CI 16.6%-25.1%). In these three studies, the mean number of D+ RBC units transfused to the D- recipients before the anti-D was detected was between 3.2 and 6.0; perhaps the alloimmunization rate is even lower for recipients of fewer D- units. Also note that the risk of D alloimmunization following a D+ platelet transfusion is even lower at 1.4%.[27] Thus, if no risk mitigation steps are performed such as the administration of Rh immune globulin (RhIg) and/or an RBC exchange transfusion with D- RBCs[28]—interventions that are not always feasible because of the patient's clinical condition, timing of the D+ transfusion, access to apheresis equipment and phenotype matched RBC units—the risk of D alloimmunization is still quite low.

3. What is the probability that a FCP will become pregnant?

Answer: approximately 86%.

The Pew Research Center's analysis of data from the US Census Bureau found that in 2016, 86% of women aged 40 through 44 had given birth at least once.[29] Similarly, in the United Kingdom, data from the Office for National Statistics indicates that 82% of women who were 46 years old (minus 1 day) in 2017 had at least one live-born child.[30] In Australia in 2011, the overall fraction of women who had ever delivered at least one baby was even lower at approximately 76%.[31] These data indicate that most, but not all, women will become pregnant at least once, and this fraction should be considered when planning on a blood product resuscitation strategy for a population that includes FCPs.

4. What is the probability that a pregnant mother will carry a D+ fetus?

Answer: about 60%.

Approximately 85% of Caucasians are D+, while approximately 92% of Blacks, and 99% of Asians and Native Americans are D+.[32] However, accounting for zygosity of the *RHD* gene, there is a 60% chance that the fetus will inherit at least one *RHD* gene from a Caucasian father. Thus, there is a 40% chance that a D-alloimmunized woman will carry a D- fetus, in which case there is no risk of HDFN caused by anti-D. Similarly, when faced with a massively bleeding Caucasian FCP of unknown D type, there is an 85% chance that she will be D+ and will not become D alloimmunized if exposed to D+ RBCs, although the context of this discussion assumes that the transfused FCP is D-.

5. What is the risk of fetal death in a D alloimmunized mother carrying a D+ fetus?

Answer: approximately 4%.

This statistic is perhaps the most (pleasantly) surprising to those outside of the maternal-fetal medicine community. The Netherlands has one referral hospital where all IUTs are performed, and a national database of recipients is maintained. Thus, accurate follow up of pregnancies that are affected by HDFN can be obtained. In a recent study of 645 fetuses that received at least one IUT because of maternal alloimmunization primarily to the D antigen in the Netherlands between 1987-2016, the overall survival was 93%.[5] Overall fetal survival increased from 79% in 1987-1992 to 96% in 2011-2016 largely due to improvements in diagnosis and management, and a reduction in the number of fetuses with severe hydrops. Thus, with modern diagnostic and therapeutic modalities for alloimmunized pregnancies, the rate of fetal death is very low indeed.

Other outcomes of HDFN are also clinically important. Another Dutch study evaluated the incidence of severe anti-D HDFN defined not only as perinatal mortality but also the need for IUT, and/or the need for post-partum RBC exchange transfusions.[33] Using this definition, this study found that the rate of severe HDFN caused by anti-D was up to 25%. Using the percentages from Questions 1-4 above and substituting 25% for the risk of severe fetal outcomes, the overall risk rises slightly to 2%. Another way to approach the consequences of maternal alloimmunization and the subsequent need for IUT is to consider that there is an approximately 5% risk of neurological problems such as cerebral palsy, deafness, and developmental delays in children who were treated with IUT due to HDFN.[34] Substituting this 5% risk of neurodevelopmental impairment for the 4% risk of fetal death produces an overall risk of 0.4%. Even so, these overall risks pale in comparison to the risk of dying from hemorrhage following a traumatic injury.

How does this risk of fetal death compare with the potential benefit of early transfusion if only D+ products are available? As discussed above, there is increasing evidence that the early intervention with blood products has a positive impact on survival in massively bleeding patients. This survival benefit is important when comparing the 0.3% overall risk of alloimmunization and fetal death to the fact that more than half of civilian preventable prehospital deaths are due to hemorrhage,[35] approximately 85% of the 30,000 preventable deaths that occur every year in the United States happen before the patient arrives at the hospital[36,37]; while in Australia, 69% of people whose major bleeding began in the community did not survive until hospital arrival.[38]

This approach to early resuscitation with blood products has been introduced into routine clinical practice in San Antonio, Texas. Emergency first responders in this city, and in some of its surrounding areas,[39] transfuse exclusively D+ low titer group O whole blood (LTOWB) to all eligible trauma patients regardless of their gender and age (minimum ≥5 years) because they historically have had very few traumatically injured D- FCPs that have required a massive

transfusion; this center demonstrated that of 124 MTP activations over a 30-month period, there was only one FCP who underwent pre-transfusion testing and was found to be D-.[40] At this center it was calculated that it would take approximately 250 years for 100 D- FCPs to receive units of D+ LTOWB during trauma resuscitation; these authors estimated that over this time period, 500 traumatically injured FCPs would die from hemorrhage if they were not transfused with D+ LTOWB.[40] The 0.3% rate of D alloimmunization and fetal death calculated above translates into fewer than one fetal death for every 300 D- FCPs who are transfused with D+ LTOWB in an emergency; using the San Antonio transfusion in trauma rate, it would take 750 years for one fetus to die from a D alloimmunization event that occurred due the transfusion of D+ LTOWB to a D- FCP during traumatic hemorrhage. During that time, the early provision of D+ LTOWB would result in saving 1500 women. Thus, it seems clear that the provision of blood products, even if they are D+, trumps the small risk of alloimmunization and fetal death.

Regardless of its etiology, time matters with massively bleeding patients and sometimes unconventional thinking should be considered if lives are to be saved. Some examples of unconventional thinking in this context include the use of group A plasma,[41] LTOWB,[42,43] and D+ RBCs. However, it is important to remember that alloimmunization can entail some morbidity, such as the potential for immune transfusion reactions and potential delays in access to compatible RBCs in the future. Communities need to calculate what levels of risk they can accept in different scenarios. Ultimately, the optimal risk mitigation step is a safe and sufficient supply of blood. However, if faced with the prospect of death from massive bleeding or the manageable risks of alloimmunization in the future, it is time to reconsider the risk of transfusing D- FCPs with D+ RBCs in the trauma and massive transfusion settings.

It is also important to consider the best transfusion resuscitation practices for children in trauma. Children who require a massive transfusion (defined in one study as >40 mL of any blood product) from events like motor vehicle accidents, falls, and homicides have a nearly 51% mortality rate[44]; this rate is more than double that of adults who have massive bleeding in trauma as mentioned above. Thus, optimizing the care of massively bleeding children by providing blood products for pre-hospital resuscitation, could have impact on outcomes. As in adult trauma resuscitation, i.e., the scarcity of D- RBCs and LTOWB, especially in the pre-hospital setting, where D+ blood products might be the only units available remains. Although the alloimmunization rate in children has not been well studied; in a cohort of over 1600 transfused children who were up to 3 years old, only two became alloimmunized (anti-M and -E),[45] while 12/909 (1.3%) transfused children who were ≥4 months to ≤17 years old and were not receiving chemotherapy produced an antibody.[46] Thus, the D alloimmunization rate in children is unknown, but based on these overall alloimmunization rates, it would be expected to be lower than in adults. For boys, the minor consequences of alloimmunization following exposure to D+ RBCs are essentially the same as for men—the potential for delayed hemolytic reactions and the delayed provision of D- blood while units are found and crossmatched. For girls, the same calculus as described above applies with the notable exception of the higher mortality rate in traumatically injured children compared to adults, which perhaps provides a greater impetus to provide potentially lifesaving blood products as early as possible in the resuscitation, even if the products are D+.

HDFN is now an almost completely treatable disease where there is access to modern obstetric services. The mortality benefit of the early intervention with blood products in massively bleeding patients is becoming clear. As such, the fear of providing D+ RBCs to D- or D type unknown FCPs should be balanced against the benefits that early transfusions provide for life-threatening hemorrhage. Massively bleeding D- FCPs, or those of unknown D type, should not be denied the same lifesaving treatments that are routinely provided to males or older women for fear of affecting a future fetus. After all, a woman cannot have a pregnancy affected by HDFN tomorrow if she dies from bleeding today. Moreover, for a woman who is already a mother, saving her life through early intervention with blood products in the case of major bleeding, while recognizing and accepting the very low risk of a future treatable condition, can improve her chances of being around to care for the children she already has.

CONFLICT OF INTEREST

JFW reports serving as a consultant in medico-legal cases related to kernicterus and as a consultant for Mallinckrodt Pharmaceuticals. The other authors have no conflicts of interest to disclose.

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