Who's afraid of incompatible plasma? A balanced approach to the safe transfusion of blood products containing ABO-incompatible plasma

Mark H. Yazer,[1] Jansen Seheult ,[1] Steven Kleinman,[2] Steven R. Sloan,[3] and Philip C. Spinella[4]

Since the early 1950s, blood banks and transfusion services have sought to identify a titer threshold for the labeling of blood components containing potentially ABO-incompatible plasma as low risk and thus less likely to cause hemolysis.[1,2] Some transfusion services have shied away from ABO-incompatible plasma transfusion altogether citing the small and difficult-to-quantify risk of an acute hemolytic transfusion reaction (HTR) or other uncommon adverse events.[3-5] There are, however, three main situations where ABO-incompatible plasma is issued by today's blood banks. First, inventory limitations have made transfusion of platelet (PLT) concentrates across ABO barriers a very common practice in the United States with up to 40% of PLT transfusions being ABO incompatible with the recipient.[6] Second, the shortage of AB donors and increasing use of plasma in trauma resuscitation protocols has led to increased utilization of group A plasma for trauma patients of unknown ABO group.[7] Third, building on the successful military experience, there has been renewed interest in cold-stored group O whole blood (WB) as the first blood component to use during civilian trauma resuscitation.[8] In addition, other potential sources of incompatible plasma include large-volume cryoprecipitate transfusions and use of CPDA-1 RBCs that contain significant quantities of plasma. This commentary explores the evidence on the safety of transfusing blood components containing ABO-incompatible plasma and reviews the strategies available to mitigate the small risk of hemolysis associated with ABO-incompatible plasma transfusions in the absence of a consensus definition for a low-titer plasma-containing product.

A SAFE PRACTICE: LESSONS LEARNED FROM THE TRANSFUSION OF ABO INCOMPATIBLE PLTs

Hemolysis after ABO-incompatible plasma transfusion is mediated by the binding of donor anti-A and/or anti-B isohemagglutinins to A and/or B antigens on the recipient's red blood cells (RBCs). The incidence and severity of hemolysis after the administration of ABO-incompatible plasma can plausibly be connected to a combination of donor-related factors (the isotype, titer, avidity, and complement-binding ability of the isohemagglutinins);[9] transfusion-related factors (mainly the volume of ABO-incompatible plasma transfused);[10] and recipient attributes including age,[11,12] weight, secretor status,[13] perhaps complement factor concentration,[14] and the nature of the underlying disease (such as whether there is active bleeding at the time of the ABO-incompatible transfusion, as well as the activity of the reticuloendothelial system).

Hemolytic transfusion reactions after ABO-incompatible PLT transfusions are uncommon events, such that the chance occurrence of a single case in a given year can markedly affect incidence rate estimates. Nonetheless, the practice of transfusing ABO-incompatible PLTs, which usually contain 300 to 350 mL of potentially incompatible plasma per apheresis unit, has proved to be relatively safe, with a reported rate of HTRs as low as 1 in 120,000 PLT transfusions using titered products, almost equivalent to the rate of the accidental transfusion of ABO-incompatible RBCs.[15-18] While two single-center

ABBREVIATIONS: HTR(s) = hemolytic transfusion reaction(s); STAT = safety of the use of group A plasma in trauma; WB = whole blood.

From the [1]Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania; the [2]Department of Pathology and Laboratory Medicine, University of British Columbia, Victoria, British Columbia, Canada; the [3]Department of Laboratory Medicine, Boston Children's Hospital, Boston, Massachusetts; and the [4]Department of Pediatrics, Division of Critical Care Medicine, Washington University in St Louis, St Louis, Missouri.

Address reprint requests to: Mark H. Yazer, MD, The Institute for Transfusion Medicine, 3636 Boulevard of the Allies, Pittsburgh, PA 15213; e-mail: myazer@itxm.org.

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studies have reported incidence rates for HTRs as high as 1 in 9700[15] or even 1 in 647,[19] these risk estimates may be biased by the absence of a titer threshold that would have prevented the transfusion of a high-titer ABO minor–incompatible product, the fact that only a single event was observed at each center during their study periods, and the relatively small total number of ABO-incompatible transfusions during their study periods (the denominator used for incidence rate calculations). In one of the studies, the authors identified one patient in 647 (0.15%) who had a febrile reaction and a positive post-transfusion direct antiglobulin test (DAT) with anti-A elutable from her group AB RBCs after the transfusion of two group O PLT units. However, it was unclear if the DAT had been positive before the transfusion and if this patient actually had clinically significant hemolysis after receipt of the incompatible PLT transfusions or if her underlying disease contributed to her clinical and biochemical changes. If she actually had clinically significant hemolysis, the risk of HTR due to ABO-incompatible PLTs could be as high as 1 in 647. However, the confidence interval around this rate is very wide due to the small sample size such that it includes an incidence rate estimate as low as 1 in 26,000.

Apheresis PLTs (usually from group O donors) have been implicated in the majority of ABO-incompatible HTRs while hemolysis after the transfusion of WB-pooled PLTs has been less commonly reported, perhaps since the total volume of ABO-incompatible plasma transfused with pooled PLTs contains approximately 60 to 65 mL from each donor, compared to 300 to 350 mL with an apheresis unit.[9,11,12,20-22] Thus, the quantity of potentially incompatible antibody contributed by any one WB PLT donor is smaller than that found in an apheresis unit.

A series of review papers have identified only 26 published cases of HTRs from around the world in adult recipients after ABO-incompatible PLT transfusions, all of which were associated with transfusion of group O PLTs to A (n = 18), AB (n = 4), or B (n = 4) recipients.[9,23,24] Apheresis PLT units (usually with high anti-A and/or anti-B titers) were implicated in the majority of these reactions whereas WB pooled PLTs were associated with only eight reactions. Even though there was clinical and/or laboratory evidence of intravascular hemolysis, all of these patients survived. These review papers also described 12 additional HTRs reported after ABO minor–mismatched PLT transfusions in pediatric patients ranging from age 9 days to 18 years and in one fetus after an intrauterine transfusion.[23] Again, all of the HTRs were associated with a group O PLT unit (the majority of which were apheresis PLTs) transfused to an A (n = 8), AB (n = 3), or B (n = 1) recipient. Three of the recipients died: an 8-month-old infant undergoing chemotherapy who received 15mL/kg of a group O apheresis unit with an anti-A titer of 128, a 2-year-old who received a group O apheresis unit with a gel anti-A titer of 32,000, and a 16-year-old patient who received a group O apheresis unit with a high anti-A titer (>8000).[21,25,26]

From the approximately 10 to 12 million PLT doses transfused in the United States between 2005 to 2015, there have only been seven fatalities reported to the US Food and Drug Administration (FDA) that implicated an ABO-incompatible PLT transfusion: five cases were associated with what the FDA termed "high-titer" group O apheresis units (anti-A titer of 2048 in one case, titer not reported in the other four cases), another case was associated with a group A apheresis unit with an anti-B titer of 2048 that was transfused to a group B recipient, and in the last case, two group O apheresis units with anti-A and anti-B titers of 128 from the same donor were transfused to an AB recipient.

Overall, hemolysis after an ABO-incompatible PLT transfusion is an uncommon event, and if units with a relatively "high-titer" isohemagglutinin are detected and not issued to patients whose RBCs express the corresponding A and/or B antigens, it follows that the hemolysis rate would decrease even further.

THE NEVER-ENDING QUEST PART 1: IN SEARCH OF A STANDARD TITER METHOD

Currently, the main strategy to mitigate the risk of an HTR after the transfusion of ABO-incompatible PLTs is the determination of the anti-A and/or -B titer in the donor unit, since the majority of reactions occur after the transfusion of a high-titer product.[16] Adoption of a titration-based risk mitigation strategy for ABO-incompatible blood products involves, first and foremost, careful consideration of the method used to measure the isohemagglutinin titers. Belin and colleagues[27] recently reviewed six studies that compared conventional saline tube testing to gel methods for the determination of predominantly immunoglobulin (Ig)-G and/or predominantly IgM antibody titers. There was significant variability in the way the titers were performed between the reviewed studies including the dilution procedures and diluent used, washing procedures for RBCs, centrifugation times, temperature and length of incubation, scoring of agglutination, and specimen type (plasma or serum) tested. Overall, gel assays resulted in more reproducible results that were approximately one to two dilutions higher compared to conventional tube methods, although the absolute difference in titer varied by study. The gel titration method also has other advantages over conventional tube testing: it can be automated allowing high-throughput screening, the gel cards can be kept for up to 1 year without the need for refrigeration, and the agglutination is stable for hours thereby allowing time to obtain a second opinion, if required—unlike in tube testing where the agglutination dissipates very quickly and the technique requires smaller

sample volumes. There are now published standardized methods for both gel and tube testing developed by the Biomedical Excellence for Safer Transfusion (BEST) collaboration and the College of American Pathologists (CAP) that attempt to reduce interobserver and interlaboratory variability.[28]

THE NEVER-ENDING QUEST PART 2: IN SEARCH OF A SAFE TITER THRESHOLD

After choosing a titration method, establishing what constitutes a low antibody titer requires some consideration of the proportion of units likely to be rejected because they have antibody titers above the threshold and are therefore suitable only for ABO group–specific transfusion, the residual risk of an HTR if a low-titer product is transfused in a minor incompatible manner, and the fluctuation of donor titers over time. Using a gel method and a titer threshold of 64, one study found that 60% of the group O PLTs tested would have been labeled as high titer.[6] In their 2004 publication, Josephson and coworkers found that using a titer threshold of 64 for IgM (buffered gel cards at room temperature) and 256 for IgG (anti-IgG gel cards) led to 28 and 39% of donor units being categorized as high titer for their respective immunoglobulin isotypes.[29] The selected titer threshold can be further refined based on ongoing audits of the percentage of donors excluded due to having high titers and the rate of HTRs associated with the selected threshold. One example of the need to change titers based on clinical experience was the case of a 65-year-old group A woman, who experienced an acute hemolytic reaction to a PLT unit that had an anti-A titer of less than 100 as determined by an automated method, leading the Scottish National Blood Transfusion Service to decrease their titer threshold to less than 50.[30]

Donor immunizing events, such as transfusion, pregnancy, or perhaps vaccinations, may result in fluctuations in isohemagglutinin titers. For example, a report described two patients who experienced HTRs after receiving apheresis PLTs from a group A donor who had previously donated more than 100 apheresis PLTs without any reported hemolytic reactions.[31] The postreaction investigation revealed that the donor had increased his intake of oral probiotic medications a short time before making the index donation, which led to an increase in his anti-B titer to 16,384. However, such significant fluctuations in donor titers over time may be relatively uncommon. In fact, a recent study described stable IgM and IgG anti-A and anti-B titers among 56 healthy adult volunteers in southern Denmark who had their antibody titers measured every 3 months over a 1-year period.[32] These results are interesting because these volunteers were free to go about their daily activities over the course of the year that might have included changing their diets or receiving vaccinations, and yet overall there were only small variations in their antibody titers during the study period. Nevertheless, because of the possibility of titer fluctuation even if it occurs uncommonly, it is probably prudent to quantify the isohemagglutinin titers in each donor unit thereby eliminating the concern about not detecting potentially significant increases in the antibody titer of units that might be issued in an ABO-incompatible manner.

There is still a lack of consensus on a standard titer method and on the definition of a low-titer ABO-incompatible product. However, as hemolysis after the transfusion of ABO-incompatible plasma is rare, choosing an acceptable titering method combined with a reasonable definition of a low-titer product (i.e., one that provides enhanced safety without compromising availability) is likely to prevent some (and probably the most severe) hemolytic reactions from ABO-incompatible plasma transfusions.

BREAKING BARRIERS: THE GROUP A PLASMA AND GROUP O WB EXPERIENCE

Due to the intermittent shortages of group AB plasma, many centers are now using group A plasma during the initial resuscitation of traumatically injured patients. As the ABO group of these patients might not be known when the group A plasma is administered, some of these units are being administered to B and AB recipients where hemolysis might occur. A survey of 61 US trauma centers conducted by Dunbar and Yazer in 2016 on behalf of the BEST Collaborative found that 69% of the respondents use group A plasma for trauma patients of unknown ABO group.[33] Among the 34 centers using group A plasma, there was substantial variation in the amount of group A plasma that could be issued; several hospitals limited the number of units that could be transfused while the majority (21/34, 62%) did not impose a limit on the number of group A plasma units for these patients. The majority (27/34, 79%) of respondents did not determine the anti-B titer in the group A plasma that was issued to trauma patients, while the others used a maximum anti-B titer of between less than 25 and less than 100.[32] The safety of the use of group A plasma in trauma (STAT) study, where 76% of the participants did not determine the titer of anti-B in the group A plasma issued to trauma patients, found no difference in early mortality, in-hospital mortality, or hospital length of stay between the group B/AB trauma recipients (n = 354) who received group A plasma during their resuscitation versus the group A trauma patients (n = 809) who also received group A plasma. In addition, there were no reports of acute HTRs among the 354 group B and AB recipients.[7] Although the STAT study is the largest study to date that examined the use of incompatible group A plasma during the initial resuscitation of traumatically injured patients, the results should be interpreted

TABLE 1. Strategies for screening apheresis PLTs, group A plasma, and group O WB donors for high-titer isohemagglutinins

Product	Source	Method	Critical titer: direct agglutination, indirect agglutination
Group O apheresis PLTs	Josephson et al.[41]	Gel	≥64, ≥256
	Cooling et al.[6]	Gel	NT, ≥128
	Quillen et al.[42]	Gel	≥250, NT
	Karafin et al.[19]	Gel	≥512
	Pittsburgh, PA[16]	Tube	≥100, NT
	UK national guidance[43]	Automated	≥100, NT
		Tube	≥128, NT
	Scottish National Blood Transfusion Service[29]	Automated	≥50, NT
	Italy[44]	Gel	≥64, 256
	Germany[44]	Tube	≥64, NT
	Norway[44]	Gel	NT, ≥250
	Sweden[44]	Tube	≥100, ≥400
	Japan[44]	Gel	NT, ≥512
Group A plasma	STAT study[7]	Tube	≥50, NT
	3 centers	Tube	≥100, NT
	1 center 13 centers	NT	
WB	Mayo Clinic, MN[33]	Tube	≥200, NT
	Pittsburgh, PA[34]	Tube	≥50, NT

with the caveat that an acute HTR after the transfusion of ABO-incompatible plasma is a rare event and definitive proof of safety will require even larger sample sizes.

The experience with cold-stored WB for civilian trauma resuscitation is also developing. Of the 30 low-titer (<200 by immediate-spin tube testing), cold-stored group O WB units transfused at the Mayo Clinic between November 2015 and September 2016, there were no reported HTRs.[27,34] At the University of Pittsburgh, the initial experience of transfusing up to 2 units of low titer (<50 by saline tube method), cold-stored group O WB for trauma resuscitation found no laboratory or clinical evidence of hemolysis among the non–group O recipients compared to the group O recipients where immune hemolysis mediated by anti-A and -B could not have occurred.[35] The maximum number of WB units available for transfusion to trauma patients has since been increased to 4 units at the University of Pittsburgh, and there is still no laboratory or clinical evidence of hemolysis among the recipients of this greater number of WB units (unpublished observations). Furthermore, the Children's Hospital of Pittsburgh transfuses up to a maximum of 30 mL/kg of the same low-titer, group O WB to pediatric trauma patients who are at least 3 years old and weigh at least 15 kg. In the more limited experience of using WB in the pediatric population, no clinical or laboratory evidence for hemolysis has been detected in the nine non-group O recipients compared to the eight group O trauma recipients of WB.

Based on the limited evidence accumulated to date, the transfusion of ABO-incompatible plasma in the form of group A plasma and low-titer, group O WB in hemorrhaging trauma patients appears to be a relatively safe practice. However, more studies will be required to provide definitive proof of safety.[36] The decision to titer group O WB when an ABO incompatibility between donor and recipient is a possibility seems reasonable given the potential for higher than usual anti-A and -B titers in group O donors.

A BALANCED APPROACH: PICK A METHOD, PICK A REASONABLE TITER THRESHOLD, KEEP CALM, AND TRANSFUSE ON

Efforts thus far have been focused on defining the optimal titration method and titer threshold for classifying a unit containing potentially ABO-incompatible plasma as low titer. However, the ability of an antibody to cause hemolysis is mediated by multiple factors apart from the titer, including antibody class, subclass, specificity, affinity, thermal range, and complement-activating efficiency. Due to the absence of a standardized isohemagglutinin titration method and the fact that some HTRs occur after transfusion of low-titer plasma-containing components, research into novel approaches to determining the hemolytic potential for these antibodies is required. The monocyte monolayer assay shows some promise in distinguishing between clinically significant and insignificant alloantibodies of IgG type.[37] Other in vitro assays, such as the recently described complement hemolysis using human erythrocytes (CHUHE) test, might also be useful in predicting the hemolytic potential of group A plasma.[38,39] However, until more clinical correlations between the results of these assays and actual recipient outcomes can be made, antibody titration is the most

accepted method available for predicting the risk of an HTR from ABO-incompatible plasma transfusions.

Apart from the titer technique, selection of a titer threshold requires some cognizance of the potential impact that the threshold will have on the available donor pool; the lower the selected titer threshold, the fewer donors that are likely to be suitable. Thus, setting the titer threshold requires a balance between lowering the risk of an HTR without excluding so many donors that it limits the supply. However, in this calculus, recipient safety must be the main determining factor. As a guide, Table 1 provides some examples of titration methods and titer thresholds that have been implemented at blood centers in developed countries. When a reasonably low-titer threshold is selected, few donors will be excluded (only approx. 20% of group O WB donors are excluded at the University of Pittsburgh where the critical titer is <50; approx. 14% of group A plasma donors are excluded using the same threshold) and no evidence of hemolysis has been reported. Transfusion services in several European countries, such as the United Kingdom,[40] are required to have a testing and issuing policy in place to avoid the transfusion of plasma-containing products from donors with high-titer anti-A and/or anti-B donors to non-group O recipients. In contrast, current AABB standards do not mandate the determination of antibody titer in potentially ABO-incompatible plasma-containing products, but these standards do require transfusion services to develop specific policies and procedures concerning the transfusion of components containing significant amounts of ABO-incompatible antibodies (Standard 5.15.4).[41] It is therefore up to individual blood centers and transfusion services to determine their preferred method of complying with this AABB standard.

Although there is still no universal consensus on the ideal method for performing anti-A and/or -B titers, or what a low-titer threshold should be, in our opinion based on reviewing the literature and our personal experience with incompatible plasma-containing products, issuing potentially ABO-incompatible products with anti-A and/or anti-B titers of less than 200 (using saline tube methods) or less than 400 (using gel methods with anti-IgG) appears to be a reasonable strategy that balances the risk of an HTR in vulnerable recipients with the need to maintain an adequate inventory of blood products. Additional unresolved issues include determining if there is a maximum volume of incompatible plasma that can be safely transfused to an individual recipient and whether each donation needs to be titered.

In the end, hemolysis after an ABO-incompatible plasma transfusion is a rare event and typically occurs from transfusing a unit with an obviously high-titer antibody. Thus, determining the titer(s) of the potentially incompatible antibody(ies) using any method available and selecting a reasonably low-titer threshold as described above will add extra protection, that is, make hemolysis even less likely, when transfusing these products to non–group O recipients. The absence of a standard titer method or a universally accepted definition of a low-titer product should not limit the use of group A plasma and group O WB. The definition of a safe titer threshold can be refined as new evidence and experiences with incompatible plasma accumulate. The transfusion and trauma communities need to collect more data on recipients who have received incompatible plasma products and develop a consensus for a safe titer threshold and method that satisfies both the immunohematologists and the clinicians. Standardizing these variables will permit the comparison of patient outcomes on an international scale and will provide a benchmark for future studies. Until that time comes, transfusion services that are considering providing potentially incompatible plasma products should pick a titer method and a reasonable titer threshold, keep calm, and transfuse on.

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Donald H. Jenkins, MD FACS, Department of Surgery, Division of Trauma and Emergency Surgery, University of Texas San Antonio, San Antonio, TX

Ernest E. Moore, MD, Department of Surgery, University of Colorado, Denver, CO

Paul Ness, MD, Johns Hopkins University School of Medicine, Baltimore, MD

Eilat Shinar, MD, Magen David Adom National Blood Services, Ramat Gan, Israel

James R. Stubbs, MD, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN

Kevin R. Ward, MD, Department of Emergency Medicine, Michigan Center for Integrative Research in Critical Care, University of Michigan, Ann Arbor, MI

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