Anaphylactic transfusion reactions

Colleen W. Gilstad

Purpose of review

Although anaphylactic reactions to blood products are rare, the incidence of allergic reactions to blood products is similar to the allergic reaction incidence to penicillin antibiotics, and therefore worthy of proportionate attention.

Comprehensive reviews and guidelines of the management of anaphylaxis currently do not include much information on blood products. Current guidelines for the specific management of anaphylactic transfusion reactions are contradictory as to the utility of anti-IgA testing and incomplete by not offering suggestions for the management of non-IgA related reactions.

Recent findings

Anti-IgA is not responsible for most reactions. Anti-haptoglobin antibodies are responsible for more reactions than anti-IgA in Japan, but the cause of most reactions is still not known. The incidence of reactions to platelets is the highest compared with fresh frozen plasma and red blood cells. Pre-storage white blood cell reduction of platelets does not decrease the incidence of reactions, indicating that white blood cell-derived cytokines are not responsible for most reactions.

Summary

The increased incidence of reactions to platelets compared with fresh frozen plasma suggests that a platelet-related factor may be responsible for many of the reactions. The possible role of platelet microparticles or activated platelet membranes, which carry a negative charge similar to ionic radiocontrast media, the major cause of iatrogenic anaphylactic reactions in the hospital, is explored.

Keywords

anaphylaxis, transfusion reactions

Curr Opin Hematol 10:419–423. © 2003 Lippincott Williams & Wilkins.

Medical Director, Armed Services Blood Bank Center and Transfusion Service, National Naval Medical Center, Bethesda, Maryland, USA

Correspondence to Colleen W. Gilstad, MD, Medical Director, Armed Services Blood Bank Center and Transfusion Service, National Naval Medical Center, 8901 Wisconsin Ave. BLDG 9, RM 1638D, Bethesda, MD 20889-0001, USA
E-mail: cwgilstad@bethesda.med.navy.mil

The views expressed in this article are those of the author and are not to be construed as the official position of the United States Department of Defense or the United States Navy.

Current Opinion in Hematology 2003, 10:419–423

Abbreviations

PMPs	platelet membrane-derived microparticles
RCM	radiocontrast media
TRALI	transfusion-related acute lung injury
WBC	white blood cell

1065–6251

Introduction

An anaphylactic or anaphylactoid reaction to blood transfusion is a rare complication that presents the clinician with a difficult management decision if a patient requires more blood products. Many clinicians may have to rely on published guidelines rather than experience for the treatment of their patients. Unfortunately, current guidelines are contradictory or in some cases not practical by recommending a testing protocol where timely test results will not be available. Also, many articles focus on tests for anti-IgA in patients' serum even though results can be expected to be negative in most cases. For this reason, a broader view of the problem in the context of other iatrogenic anaphylactic reactions in the hospital may be useful.

Proposed mechanisms of anaphylaxis

Anaphylaxis is generally recognized as a rapid, dramatic, and potentially catastrophic reaction to immunologically foreign substances in sensitized persons. It is usually recognized by a combination of physical signs including hypotension, bronchospasm, edema, gastrointestinal symptoms, and skin rash. Although a distinction between anaphylactic (specifically mediated by IgE) and anaphylactoid reactions (clinically indistinguishable from anaphylactic reactions but not mediated by IgE) has been made, it is common practice to use anaphylaxis to describe both syndromes [1]. There are believed to be four major mechanisms responsible for anaphylactic reactions to foreign substances [1]. The first and classic mechanism involves an IgE-mediated reaction against foreign proteins, of which bee sting and food allergies are the classic examples. Another involves IgE-mediated reactions against protein-hapten conjugates, of which penicillin allergy is the classic example. Another involves complement activation and generation of endogenous anaphylotoxins, which is the postulated mechanism for high titer IgG antibody to anti-IgA causing reactions to blood products containing IgA [2]. Finally, direct activation of mast cells or complement is the proposed mechanism behind anaphylactic reactions to ionic radiocontrast medium. Distinct from these four proposed mechanisms of anaphylactic reactions, blood products are also postulated to cause reactions by containing preformed, exogenous anaphylatoxins, such as histamine, C3a, and C5a.

Risks of anaphylaxis to blood products compared with other iatrogenic causes

Estimates for the incidence of anaphylactic transfusion reactions have ranged from 1 per 170,000 to as high as 1

per 18,000 blood products transfused. [3]. These estimates, based on 1970s data when the entity of transfusion-related acute lung injury (TRALI) was not described, may be questionable because of the concern that TRALI, another adverse reaction with prominent respiratory symptoms, was being misdiagnosed as anaphylaxis. However, it seems from a series of lookback cases from a multiple-unit donor implicated in TRALI, that TRALI-like reactions were not often misdiagnosed as anaphylaxis [4•].

More recent studies have refined earlier estimates to provide component-specific risk estimates and indicate that platelet components cause the highest rate of allergic and anaphylactic reactions, followed by fresh frozen plasma. Sixteen "anaphylactoid or anaphylactic" reactions were reported in the year 2000 to the Quebec hemovigilance system, which accounted for an incidence of 1:23,148 RBC, and 1:1598 platelet transfusions [5••]. A 9-year retrospective review of all transfusion reactions reported to the Cleveland Clinic transfusion service of an estimated 1,125,846 components transfused found "severe allergic" reactions to have occurred in 1:53,612 blood components, which accounted for 1:9630 platelets, 1:28,831 FFP, and 1:57,869 RBC transfusions [6•].

To put these figures in the perspective of anaphylactic reactions to other iatrogenic causes, the most common iatrogenic cause of anaphylactic reactions in the hospital is ionic radiocontrast media, which has an estimated risk of 1 in 450 exposures. The second most frequent cause, penicillin class antibiotics, induces anaphylaxis at an incidence between 1:2500 and 1:6000 exposures and is estimated to cause 400 deaths per year [7]. The risk of anaphylactic reactions during surgery is estimated to be 1 per 13,000 operative procedures and these reactions are most often attributable to muscle relaxants, which account for 50 to 70% of the total reactions. Blood products are only very rarely implicated [8]. Of note, despite the seemingly 10-fold increased rate of anaphylactic reactions to penicillin antibiotics compared with all blood products, an earlier study of allergic skin reactions in medical inpatients found that there was a 2.2% incidence of allergic reactions to blood products compared with 5.1% to amoxicillin, 3.3% to ampicillin, and 2.1% to semisynthetic penicillins [9].

Diagnosis of IgA deficiency in managing anaphylactic transfusion reactions

Despite the fact that blood products, especially platelets, seem to have an incidence of allergic reactions comparable to penicillin antibiotics, major consensus recommendations on treating patients with previous anaphylactic reactions do not include any recommendations for blood product hypersensitivity [10]. This is likely related to the fact that the cause of most of the reactions has remained elusive, and contradictory information is available on the risk of reactions to IgA-deficient patients with anti-IgA.

Anti-IgA has been the focus of articles on anaphylactic transfusion reactions since it was first described by Vyas *et al.* in 1968 [11]. Since that time regional registries of IgA-deficient donors have been established in the US, Canada, Europe, and South America [12•]. Adequate amounts of IgA-deficient blood products have been made available for IgA-deficient patients undergoing liver transplantation [13]. Because this infrastructure exists, it does not seem unreasonable that an AABB Press textbook on transfusion reactions includes the recommendations that "when a patient experiences an anaphylactic or severe anaphylactoid transfusion reaction for the first time, the pretransfusion serum must be screened for anti-IgA" and "If an anti-IgA is detected, a lifelong commitment to transfusion with only IgA-deficient blood components is made" [3].

Most reactions are not related to anti-IgA, however. In a large study of sera from patients with a history of anaphylactic transfusion reactions, anti-IgA was detected in only 65 of 359 (18%) of the patients and anti-IgA was detected in1 of 1200 random blood donors [14]. Of 4138 nonhemolytic transfusion reactions reported to the Japanese Red Cross between May 1993 and December 2000, 367 were felt to be immediate-onset anaphylactic reactions, and haptoglobin deficiency was "approximately six times higher than the prevalence of selective IgA deficiency." Anti-haptoglobin antibodies were found in these patients and the reactions attributed to them [15•]. Finally, in the year 2000 in Canada, none of 23 allergic reactions reported to Health Canada appeared to be related to anti-IgA and only 1 of 16 severe allergic reactions in the Quebec hemovigilance system appeared to be related to anti-IgA [5••].

While it is clear that testing for anti-IgA will not be helpful in establishing a requirement for IgA-deficient blood products in most cases, there also remains a question of what one should do if it is detected, especially if the antibody is of limited specificity. Reported practice ranges from support with IgA-deficient blood products for a liver transplant patient with an anti-IgA of limited specificity and no history of previous transfusion [13] to continued infusions with IgA-containing IVIG in a patient with known high titer anti-IgA [16]. The basis of the latter practice is the fact that anti-IgA can be detected in as much as 25% of patients with common variable immunodeficiency of which the majority tolerate repeated infusions of IVIG without adverse reactions. The basis of the former practice is a perception of prudence in attempting to reduce risk by avoidance of a possible offending allergen. There obviously is a need for careful consideration in management decisions in-

volving a possible lifelong requirement on a rare product rather than the reliance on a single imperfect test.

Vyas *et al.* recognized very early that there were two distinct groups of patients with anti-IgA and carefully described the distinction between "class specific" and "limited specificity" anti-IgA [11]. The first group of patients suffered severe anaphylactic reactions, had no detectable serum IgA, and produced very high titers of anti-IgA that reacted with all IgA paraprotein-coated red blood cells (class specific). The second group consisted of generally multiple transfused patients with detectable levels of serum IgA, low titers of anti-IgA that reacted with only some IgA paraprotein coats and not others (limited specificity), and who had only suffered urticaria or other milder reactions to blood products [17]. Although some authors have since contested this observation in citing a death associated with an anti-IgA of limited specificity [3], careful readers of the citation will note that the autopsy findings indicated that the cause of death was myocardial infarction. Thus it would appear that determination of a patient's IgA level can be helpful in stratifying a patient's risk of future severe anaphylactic transfusion reactions. In Japan, however, it may not be inappropriate to forego testing for IgA levels or anti-IgA until haptoglobin deficiency is ruled out.

As sensitive methods to detect low levels of IgA, anti-IgA, or haptoglobin are not available in most hospitals, some clinicians may be faced with a patient who needs an urgent transfusion before results of this testing are available. As most other described causes of anaphylactic transfusion reactions besides IgA are also plasma proteins, if the urgent need is for a cellular blood product, in most cases washed red blood cells and platelets should be available. Washed components can be provided while waiting for testing of IgA levels and anti-IgA. If the need is for a plasma product, however, the decision is more difficult. Information that may aid this decision is presented next.

Activated platelet membranes or platelet-derived microparticles as possible cause of anaphylactic transfusion reactions

Based on reaction incidences, it appears that most allergic and anaphylactic reactions are due to substances present in the highest levels in platelets. If the substances were constituent plasma proteins, such as haptoglobin or IgA, one would expect that the incidence of reactions to FFP would be highest, or that the incidence of reactions to FFP and platelets would be similar. A theoretical cause for many reactions to platelets, febrile or allergic, is white blood cell (WBC)-derived cytokines that accumulate in the plasma portion during the condition of room-temperature storage under continuous agitation. However, two recent studies from Canada comparing allergic and febrile reaction rates to platelets that have either been pre-storage leukocyte reduced or plasma-removed by one of two different methods indicate that most allergic reactions to platelets are not likely caused by cytokines released from WBCs during storage. Both studies showed no benefit of pre-storage WBC reduction in reducing allergic reaction rates [17,18]. In the study of acute reactions in pediatric patients, there was a 5% incidence of allergic reactions to standard platelets and a 6% incidence to pre-storage WBC-reduced platelets [18]. In the study in adult patients there was a 4.1 and 4.8% incidence of allergic reactions to pre-storage WBC-reduced whole blood derived and apheresis platelets respectively [19]. This compares with a 2.7% incidence of reactions to post-storage WBC-reduced platelets in a previous study of the same type of patient population [20]. Interestingly, in the pediatric population study, where the plasma-removed platelets were resuspended in ABO-compatible thawed FFP, the allergic reaction incidence was 6%, similar to the reactions to nonplasma-removed platelets. However, in the study of adult patients, in which the platelets were resuspended in a nonprotein containing artificial platelet storage solution, there were no allergic reactions in the plasma-removed arm compared with the 4.1 and 4.8% allergic reaction incidence in the nonplasma-reduced, whole blood-derived, and apheresis pre-storage WBC platelet arms. These latter results are consistent with a plasma protein basis for the reactions, such as IgA or haptoglobin, but do not account for why platelet reactions occur more frequently than FFP reactions.

It has been proposed that platelet membrane-derived microparticles (PMPs) may be responsible for the high incidence of reactions to platelet concentrates [21]. Although these authors did not present evidence in support of their hypothesis, the results of the two Canadian studies would be consistent with the theory that activated platelet membranes or microparticles caused allergic reactions. Platelet microparticles are present in a significant amount in FFP [22] and would be expected to be at higher levels in stored platelet concentrates. They would not be expected to be reduced significantly by pre-storage WBC reduction. Removing the plasma supernatant would be expected to provide a more noticeable benefit if the platelets were resuspended in a solution without a significant amount of PMPs as opposed to FFP. A prospective trial has also found that buffy coat-reduced red blood cells (BC-RBCs) were associated with fewer allergic reactions compared with red blood cells prepared by the platelet rich plasma method [23]. Again, it is known that BC-RBCs have lower platelet content than standard RBCs, in addition to fewer WBCs [24].

Like ionic contrast media, activated platelets and platelet microparticle membrane surfaces are negatively charged. In platelets this charge is due to externalized phosphatidyl serine and phosphatidyl ethanolamine on

their surfaces, which are capable of activating the coagulation cascade [25] and would be expected to be capable of activating the complement cascade. The example of ionic radiocontrast media (RCM) indicates that there may be some patients who are more susceptible to activation of anaphylaxotoxins by the high, hyperosmolar content of negatively charged molecules in these media, and that these reactions seem to occur in the absence of an antigen-antibody reaction. Patients known to be at the greatest risk for anaphylactic reactions to RCM are those who have experienced a previous reaction. Other patients at increased risk are those receiving β-adrenergic blocking agents and ACE inhibitors. Temporarily stopping β-blockers and ACE-inhibitors and premedication are acknowledged as valid management schemes for high-risk patients. A successful emergency pretreatment protocol for patients with a history of prior anaphylactoid reaction to RCM who must undergo an emergency radiographic procedure consists of 200 mg hydrocortisone given IV immediately and every 4 hours until RCM is administered and 50 mg diphenhydramine IM 1 hour before RCM administration [10]. Further studies elucidating an association of RCM anaphylaxis risk and blood product risk would be helpful in determining if these protocols would be helpful in patients who have suffered an anaphylactic transfusion reaction and need additional blood products emergently.

If negatively charged activated cellular membranes were implicated in an anaphylactic transfusion reaction, another management option for patients who need fresh frozen plasma would be solvent-detergent treated plasma (SD Plasma). This product does not contain negatively charged platelet microparticles with procoagulant platelet factor 3 activity [26•]. A suggestion has been made previously that this product is associated with fewer acute reactions [27] and there is a case report of a patient who became intolerant of both FFP and cyrosupernatent due to severe allergic reactions but tolerated SD Plasma without difficulty [28]. Additional prospective studies focused on allergic and anaphylactic reactions in patients in whom IgA deficiency and/or haptoglobin deficiency have been ruled out would be needed to show definitively the benefit of SD Plasma compared with FFP in patients susceptible to allergic and anaphylactic reactions. Unfortunately, this product is no longer available in the US.

Conclusion

In conclusion, the treatment of patients with previous anaphylactic transfusion reactions is complicated because the cause for most reactions is still unknown. Despite this fact, lessons can be learned from the general problem of anaphylaxis. It may be useful if patients in whom an IgA-associated reaction has been ruled out were referred to allergists and immunologists so that the relation of anaphylaxis to blood products to other allergies and hypersensitivities could be evaluated. Currently, allergic reactions to blood products are not often included in reviews by allergists and immunologists, although reactions to radiocontrast media are well covered. Considering that allergic and anaphylactic reactions to platelets occur at a similar incidence per exposure as penicillin, platelet reactions are worthy of attention and further study.

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