The Evaluation and Management of Platelet Refractoriness and Alloimmunization

Eduardo Delafior-Weiss and Paul D. Mintz

The arrest of hemorrhage associated with an increase in the patient's platelet count after blood transfusion was first reported by Duke in 1910. It was not until the 1960s that clinical studies showed that therapeutic platelet transfusions decreased fatal hemorrhagic complications in thrombocytopenic patients and that prophylactic platelet transfusions reduced episodes of bleeding. More recent reports have suggested that a threshold of 10,000/\mu L for prophylactic platelet transfusion is equivalent to 20,000/\mu L in the absence of additional complicating clinical factors such as platelet dysfunction, associated coagulopathy, or primary defects of vascular integrity. The hemostatic benefit of platelet transfusion is presumably mediated through an increase in the posttransfusion platelet count above a target level, and claims that platelet transfusion may be beneficial even in the absence of such an increase are not commonly accepted.

DEFINITION OF REFRACTORINESS

Platelet refractoriness is empirically defined as a lack of response in posttransfusion platelet increments after 2 or more consecutive transfusions of an adequate dose of allogeneic platelets. Refractoriness is due to the shortened survival of the transfused platelets in the recipient's circulation. Historically, it has been described in 20% to 60% of patients who have received multiple platelet transfusions. The causes of platelet refractoriness can be grouped into immune and nonimmune causes.

The percent platelet recovery (PPR) after platelet transfusions is the percentage of transfused platelets circulating at the time the count is determined and is calculated by the following formula:

$$\text{PPR} = \frac{(\text{platelet increment per } \mu L)}{(\text{body surface area in square meters})} \times (\text{weight in kg}) \times (\text{blood volume as } 75 \text{ mL/kg}) \times 100 \text{ (for percent)}$$

The posttransfusion platelet count is dependent on the pretransfusion platelet count, the dose of platelets transfused, and other factors that affect the recovery, both technical and clinical. In individuals without splenomegaly, one third of radiolabeled autologous platelets are reversibly pooled in the spleen at any given time, whereas two thirds remain in the circulation, so adjustments to the recovery need to be made. Recovery of autologous platelets is on the order of 66 ± 8% and approaches 100% in asplenic individuals. Recovery is modestly reduced in thrombocytopenic patients with counts below 50,000/\mu L to approximately 50% ± 22%.

Another measurement of platelet transfusion recovery in the clinical setting is the posttransfusion corrected count increment (CCI). The CCI is calculated as follows:

$$\text{CCI} = \frac{(\text{Platelet increment per } \mu L)}{(\text{body surface area in square meters})} \times (\text{volume of product in mL})$$

From the CCI, the formula for the calculation of an effective dose (ED) of platelets is derived from the following formula:

$$\text{ED(} \times 10^{11}) = \frac{(\text{desired PLT count increment per } \mu L)}{(\text{expected corrected count increment})} \times (\text{body surface area in square meters})$$

The actual units of the CCI are (square meters)/\(\mu L\times 10^{11}\), although as an index it is typically written without units. The CCI between 10 minutes and 1 hour posttransfusion is used typically to determine the adequacy of response to platelet transfusions. The expected posttransfusion CCI between 10 minutes and 1 hour is greater than

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PLATELET REFRACTORINESS AND ALLOIMMUNIZATION

7,500, representing recovery of at least 20% to 30%. Values below these have been associated with accelerated platelet destruction. Although occasionally low CCI or percent recoveries occur for a variety of reasons other than refractoriness, poor responses to at least 2 sequential transfusions of an adequate dose of platelets is considered evidence of platelet refractoriness. Repeatedly low CCIs between 10 minutes and 1 hour posttransfusion are generally attributed to an immune cause, although in some alloimmunized patients good increments can still be achieved with incompatible platelets. In some patients with other reasons for accelerated destruction, the CCI at these times may be low. A CCI measured 18 to 24 hours after the transfusion of platelets is usually approximately 60% of the 1-hour CCI and should be greater than 4,500, equivalent to a recovery greater than 15%. A reduced CCI at 18 to 24 hours after a normal CCI at 1 hour has been interpreted as representing evidence of increased consumption owing to nonimmune clinical causes, although in some patients this can represent immune destruction.

The maximal lifespan of reinfused autologous radiolabeled platelets is approximately 9.5 ± 0.6 days, with 85% removed by senescence. A fixed number of platelets are lost at random, presumably maintaining the vascular integrity. Overall survival of platelets is decreased proportionally to the degree of thrombocytopenia. When the platelet count is greater than 100,000/µL, platelet life span is independent of the count, but life span is modestly reduced in patients with counts between 50,000 and 100,000/µL to 7.0 ± 1.5 days, and markedly reduced when platelet counts fall below 50,000/µL to 5.1 ± 1.9 days. A fixed number of approximately 7,100 platelets/µL/d is consumed. Because this represents only 18% of the normal rate of platelet turnover (41,200 platelet/µL/d), the fixed platelet consumption does not have a significant effect on overall platelet survival when counts are over 100,000/µL. However, as the platelet count decreases below 100,000/µL, a larger proportion of platelets are devoted to daily endothelial support and overall platelet lifespan decreases.

The importance of precise timing of samples for correct estimation of the CCI has been shown by del Rosario and Kao, in a study in which the investigators used the average reduction rate of 800 platelets/µL/h to make approximations to the pre-transfusion or posttransfusion counts when these were not available. This study underscores the importance of obtaining platelet counts immediately before transfusion and 10 minutes to 1 hour posttransfusion.

Although platelet refractoriness in individual patients can be attributed to single identifiable clinical factors, including fever, neutropenia, disseminated intravascular coagulation (DIC), and sepsis/infection, in many cases it is multifactorial, and no single clinical factor is an accurate predictor of posttransfusion platelet increments across patients.

NONIMMUNE CAUSES OF REFRACTORINESS

Platelet Quality

When the posttransfusion platelet count does not increase as expected, one possibility is that an inadequate dose of platelets was administered as a result of platelet loss due to washing or filtration. Although most studies have found that leukoreduction filters result in the loss of less than 10% of apheresis platelets and 20% ± 9% of pooled platelets, such losses may be independently associated with decreased posttransfusion CCI. The platelet dose should be adjusted to the patient’s blood volume, and some patients require proportionally more platelets to achieve adequate increments. Other factors that may detrimentally affect the quality of the platelets during storage include pH lower than 6.2, incorrect storage temperature, and mode of agitation. Gamma-irradiation of platelets with 25 Gy does not affect platelet function or posttransfusion survival. However, in the Trial to Reduce Alloimmunization to Platelets (TRAP) study, ultraviolet B (UVB) irradiation at dosages used to prevent alloimmunization (1.5 J/cm²) was independently associated with lower posttransfusion CCIs.

Platelet Age

There are conflicting reports regarding the benefit of fresh platelets. In one study, patients with infection, DIC, or splenomegaly were refractory to older platelets but not to fresh platelets. The possible advantage of fresher platelets in improving the response to platelet transfusions in patients with nonimmune refractoriness has been attributed to activation of platelets during storage.
study, the proportion of activated platelets in 5-day-old platelet concentrates was 15% to 20%, and these were cleared more rapidly from the circulation after transfusion than were fresher platelets.\textsuperscript{25} After an initial phase of splenic sequestration and later release to the circulation, some transfused platelets may recover their normal function and lose evidence of activation within 24 hours after transfusion.\textsuperscript{26} In several studies, recoveries were 10% to 59% higher with fresher platelet products, usually in those patients with fever, DIC, or splenomegaly.\textsuperscript{22,27} In the TRAP study,\textsuperscript{19} transfusion of platelets stored for less than 48 hours resulted in greater posttransfusion increments. The criteria for diagnosing platelet refractoriness in this study included failure to respond to fresh or ABO-matched platelets as an initial therapeutic maneuver in refractory patients. Slichter et al\textsuperscript{28} have reported the preliminary results of a small prospective randomized trial comparing fresh and stored apheresis and pooled platelet concentrates. A decrease in the viability of stored platelets became statistically significant only after 5 days of storage for both products. As a practical matter, the freshest platelets available for transfusion at most institutions may be 1 to 2 days old because of transmissible disease testing and shipment.

**Clinical Conditions**

Platelet refractoriness most commonly results from clinical conditions associated with accelerated platelet consumption. These may coexist with alloantibody-mediated refractoriness.\textsuperscript{15,17} Splenomegaly, DIC, amphotericin B therapy, bone marrow transplantation, veno-occlusive disease of the liver, and graft-versus-host disease have been reported to reduce platelet recovery.\textsuperscript{6,15,29-32} In patients undergoing hematopoietic stem cell transplantation, poor posttransfusion CCIs at 16 hours were significantly correlated with high total bilirubin, total body irradiation, high serum tacrolimus, and high serum cyclosporin by multivariate analysis.\textsuperscript{32} A multivariate analysis of clinical factors associated with decreased posttransfusion increments in the TRAP study showed fever, infection, bleeding, splenomegaly, gamma-irradiation, concurrent amphotericin B therapy, as well as a history of previous pregnancy in women, to be independently associated with decreased CCIs.\textsuperscript{19} Those transfusions associated with moderate to severe transfusion reactions were also associated with lower 1-hour CCIs.\textsuperscript{33}

When alloantibodies cannot be demonstrated by the laboratory and fewer than 3 weeks have elapsed since starting chronic transfusion therapy in patients without a history of previous exposure to HLA antigens by transfusion, solid organ transplant, or previous gestations, nonimmune clinical refractoriness is the likely cause. Although platelet refractoriness in individual patients can be attributed to single identifiable clinical factors, in many cases it is multifactorial, and no single clinical factor is a predictor of posttransfusion platelet increments across patients.\textsuperscript{17}

Although fever has been implicated in decreased platelet recoveries, it is unclear whether the sepsis, DIC, or the antibiotic treatment associated with fever rather than the fever per se are the cause.\textsuperscript{16,15,34,35} There is no evidence that decreasing fever with antipyretics will improve recoveries. Treating the underlying cause of fever and control of DIC may be of value at improving the platelet counts.

**IMMUNE CAUSES OF REFRACTORINESS**

**ABO Incompatibility**

There is a highly variable ABH expression, greater than 20-fold, on the surfaces of platelets of different persons,\textsuperscript{36} and only 7% of non-group O platelets express high levels of A or B antigens as determined by enzyme-linked immunosorbent assay and immunoblotting studies. Expression correlates with the levels of glycosyltransferase in the serum of the donor. In contrast to red cells, which express type 2 ABH chains, platelets express equal amounts of type 2 and type 1 chains.\textsuperscript{37}

Several studies have addressed the significance of ABO group compatibility in the response to platelet transfusion.\textsuperscript{38-41} In recipients with high titers of anti-A or anti-B isoagglutinins (eg, >64), ABO-incompatible platelet transfusions may consistently fail to produce adequate responses,\textsuperscript{42} but incompatible transfusions have been reported to be as effective as ABO-identical platelets in patients with lower titer isoagglutinins.\textsuperscript{43} In one report, CCIs were higher in patients who received ABO identical pooled platelets, intermediate in those who received ABO plasma incompatible platelets, and lowest in recipients of ABO major incompatible concentrates.\textsuperscript{41} Aster\textsuperscript{38} reported that the mean recovery of radiolabeled A\textsubscript{1} platelets transfused...
into O recipients was only 19% and that of A1B platelets transfused to O recipients only 8%, as compared with recovery of 63% observed when ABO-compatible platelets were transfused. In the same study, transfusion of incompatible group B platelets resulted in recoveries similar to those of compatible transfusions. ABO antigen density on the platelet surface may influence the result of transfusions, because group A2 platelets express approximately 40-fold less A antigen than A1 platelets and may provide good recoveries in group O patients even in recipients with high titers of anti-A isoagglutinins.44 Transfusion of ABO-incompatible donor plasma also may result in reduced platelet recoveries. ABO incompatible donor plasma in platelet products result in poor responses presumably from the formation of circulating immune complexes (CIC) with the soluble A and B substance in the recipient's plasma with resultant increased platelet clearance.40 Based on the available clinical evidence, a trial of platelet concentrates ABO-compatible with recipient plasma to refractory patients with isoagglutinin titers above 64 is reasonable and may result in adequate CCI.49,41 This practice defines the role of ABO incompatibility in particular patients and may be all that is necessary.

HLA Incompatibility

HLA antibodies are usually detected by lymphocytotoxicity testing. The percentage of panel cells to which the patient has developed HLA antibodies is called the panel reactive antibody (PRA) level.45 PRA may be used to screen patients receiving chronic transfusion therapy, and increases in PRA levels occurring over time may be used to predict alloimmune refractoriness.45-46 Reactivity with over 70% of the panel lymphocytes is the usual cutoff used in the clinical setting to diagnose alloimmunization.

Fewer than 50% of refractory patients have evidence of platelet or lymphocytotoxic (LCT) HLA antibodies.47,48 Most studies have shown a clear relationship between the presence of HLA LCT antibodies and concomitant platelet refractoriness,12,35,49 although in 1 series only 30% of all alloimmunized patients were refractory to platelet transfusion.50 Platelets express 73% of the whole blood load of class I HLA-A and HLA-B antigen,51 but they do not express class II HLA antigens. Platelets alone are a very weak stimulus for the formation of antibodies to HLA class I antigens, because alloantigen recognition usually requires expression of both class I and class II HLA antigens, found on the surface of donor leukocytes. Residual donor leukocytes in red blood cells or platelet concentrates provide a source of antigen-presenting cells (APC).52 Leukoreduction to less than 1 to 5 x 10^9 per transfusion minimizes the APCs in the transfused product and decreases the total antigen load, shown in various studies to be effective in preventing alloimmunization and refractoriness to platelet transfusion.50,53,54 Ultraviolet B irradiation abolishes APC stimulation in mixed lymphocyte cultures and may cause specific unresponsiveness to HLA antigens.55 Leukoreduction and UV-B irradiation were equivalent in preventing alloimmunization, as shown in the TRAP study.50 The rate of alloimmunization was not statistically different between recipients of leukoreduced platelets, 18%, and recipients of UV-B irradiated platelets, 21%, as opposed to 45% in patients receiving untreated blood products. Refractoriness was lower in the intervention arms: 3% and 5% in recipients of leukoreduced and UV-B irradiated products, respectively, compared with the controls (13%). In a separate prospective randomized study of patients selected for low-risk histories for alloimmunization (not previously exposed to HLA antigens), a reduction in alloimmunization from 42% to 7% was observed with leukoreduced blood components.54 Primary alloimmunization to HLA antigens occurs at a median of 3 to 4 weeks (range, 2 to 56 weeks) after the first transfusion in those who receive multiple transfusions.55 Patients with previous exposure to HLA antigens are at high risk to develop alloimmunization and platelet refractoriness and may do so earlier than patients without such history.46,56 In the absence of previous transfusion, alloimmunization develops in 4% of women after one pregnancy and 26% after four pregnancies.57 In the TRAP study, leukoreduction or UV-B irradiation reduced the risk of HLA-alloimmunization even in patients with previous exposure to HLA alloantigens.50 In contrast, Sintnicolaas et al46 found that leukoreduction did not prevent secondary HLA-alloimmunization (43% vs 44%) or platelet refractoriness (41% vs 29%, P = .52) in patients with a history of pregnancy in a randomized prospective study. When preformed alloantibodies are present before the current course of transfusion.
they tend to persist, whereas de novo antibodies are more likely to be transient.58 Patients receiving high-dose steroids may have their HLA-alloimmunization delayed to a mean of 7 to 8 weeks (range, 2-15 weeks).49,59

Selection of HLA-matched platelets. Selection of platelets for transfusion based on HLA matching improves posttransfusion platelet recovery in patients with platelet refractoriness due to alloimmunization to HLA antigens.47,60 Daly et al12 reported significantly improved CCIs by transfusing HLA-matched products to patients who had LCT antibodies and poor 1-hour CCIs to pooled platelets. Peters et al61 studied the kinetics of HLA-matched 1111n-labeled allogeneic platelets in 5 patients with alloimmune refractoriness and found that recovery at 1 hour postinjection and median platelet life span improved with HLA matching.

HLA antibodies may be classified in 2 groups: those that recognize only an epitope in a particular HLA allele (private epitopes), such as HLA A2 or HLA B12, and those that recognize more than 1 gene product. In the latter group, there are antibodies that may recognize structurally similar epitopes in different gene products or identical epitopes present in different alleles (public epitopes). Different epitopes that are sufficiently similar to be recognized by a specific HLA alloantibody are said to belong to a cross-reactive group.

Most patients who develop alloimmunization are broadly immunized to class I HLA antigens, and only a minority of refractory patients have clear-cut specificities to private class I antigens.62 This broad reactivity is not caused by multiple alloantibodies but instead is usually attributable to 1 or 2 antibodies directed against public specificities present in a relatively large percentage of the population. For example, Bw4 and Bw6 are public antigens encoded by a diallelic system. These antigens are associated with 2 different sets of HLA-B antigens. Special techniques such as binding assays using labeled antiglobulin reagents may be required to detect these antibodies.

HLA matching requires knowledge of the patient and prospective platelet donor HLA phenotypes. The principles of selecting compatible platelet products are based on (1) Selecting a donor with an HLA phenotype identical to the recipient (or not expressing any antigens other than those present in the recipient), or selecting crossmatch-compatible platelets; (2) Selecting a donor with partial identity to the recipient but possessing nonidentical antigens that are considered to be cross-reactive and not immunogenic to the recipient; (3) identification of antibody specificities and selection of donors who lack the corresponding antigen; (4) finding selectively mismatched donors for those antigens that are known not to be strongly expressed in donor platelets or for which expression is variable.

For HLA-alloimmunized patients matched to private antigens, prospective donors are classified based on the number of antigens identical to the recipient (Table I). Platelet count increments with A and BU matches are equivalent and superior to C and D matches in alloimmunized refractory patients.60,63 One study63 found that CCIs with BX matches were lower than with A and BU matches but higher than those with C and D matches. Overall, only 80% of alloimmunized clinically stable patients benefit from fully HLA-matched products.64 Failure rates with platelet transfusions selected using CREGs has been reported to be as high as 41%.61 Some transfusions within CREGs are more successful than others. Bidirectional transfusion within donor-recipient cross-reactive pairs A1/A11, A2/A28, B5/18, and B7/B22 resulted in good platelet increments, whereas A1/A3, A3/A11, B5/B15, B5/B17, B8/B14, B12/B21, and B7/B27 did poorly.55

Reasons for the failure of HLA-matched transfusions include undiagnosed clinical factors, alloimmunization to platelet-specific or minor histocom-
Platelet refractoriness and alloimmunization

Platelet refractoriness and alloimmunization demonstrates in two thirds of patients who lose their HLA alloantibodies and may explain this phenomenon. Patients who demonstrate alloimmune refractoriness deserve a trial of unmatched platelets at intervals after the diagnosis of refractoriness. Serial determination of LCT or platelet antibody may guide this therapy.

Platelet selection based on specific HLA antigen mismatch. Characterization of the patient's antibody may be useful in certain circumstances to choose donors by selective mismatch in patients who are less broadly immunized. For example, patients who develop antibodies against a single HLA class I antigen (e.g., HLA A2) may receive effective platelet transfusions specifically selected to be negative for the HLA A2 antigen. Pooled platelets, some of which would be expected not to express the antigen, also may be effective. In practice, this may be tried if it is difficult to find good HLA matches for a particular recipient and partially matched transfusions are unsuccessful.

Transfusing HLA antigen-positive platelets in the presence of HLA antibody. There are 50,000 to 120,000 HLA molecules per platelet. Expression of some of the class I HLA antigens on the platelet surface may vary by a factor of 35-fold for HLA-B12, 8-fold for HLA-B8, 32-fold for Bw4, and 20-fold for Bw6. In many patients with antibody to HLA B12, transfusion of HLA-B12 antigen-positive platelets may result in adequate responses. Expression of B12 is enhanced when A11 is also present, but decreased when A2, A3, or Aw28 are present. Expression of Bw4 is stronger when associated with B5 or B27, and weaker with B13. Expression of Bw6 is stronger with B7, B15 or B35, but weaker with B8 or B14. Platelets with low antigen expression may not be efficiently destroyed by the antibody. In one study, 69% of immunized patients responded to HLA-B12 antigen-positive platelets. In selected refractory patients, it may be possible to use this information to select among incompatible platelets for transfusion, if compatible products are not available.

Return to unselected platelets. LCT HLA antibodies may be transient. They have been reported to disappear in 40% of patients after 1 week to several months, despite continued platelet transfusions, and previously refractory patients have regained good responses to unmatched platelets for periods from 2 weeks to 36 months. Other studies have described similar findings. Development of anti-idiotypic antibodies reactive with the variable regions of HLA antibodies has been demonstrated in two thirds of patients who lose their HLA alloantibodies and may explain this phenomenon. Patients who demonstrate alloimmune refractoriness deserve a trial of unmatched platelets at intervals after the diagnosis of refractoriness. Serial determination of LCT or platelet antibody may guide this therapy.

Selection of platelets based on platelet cross-match. Ordering HLA-matched platelets does not guarantee an adequate match. In one study, 43% of such products were BX or C matches. The rationale for platelet cross-matching is to select a compatible platelet concentrate irrespective of the nature of alloimmunization (i.e., to HLA or platelet-specific antigens). Platelets compatible with the recipient's serum in vitro are selected from single donor platelet units available at the time of testing the inventory. Because ABO major incompatibility often leads to an incompatible cross-match, only ABO-compatible platelet units should be cross-matched.

Platelet cross-matching has the advantage of allowing selection of platelets from a larger pool of donors who otherwise would have not been selected because either they are poor matches (BX, C, or D) or their HLA type is unknown. Some blood centers include the HLA type of the donor, if known, on all single-donor platelets. This can guide the hospital transfusion service in selecting products to cross-match. Even in highly alloimmunized patients, 5% of unselected screened donors may be compatible by cross-match.

In most studies, cross-matching has been found to be equivalent to HLA matching in terms of predicting adequate responses to platelets transfusion. The sensitivity and specificity of cross-matching to predict good responses in patients have been reported to be greater than 80% in clinically stable patients. Although selection of cross-matched platelets usually results in adequate recoveries, in one study this strategy was inferior to HLA grades A and BU matching. Friedberg et al observed equivalent results with cross-match and HLA match, although HLA matching benefited only the subgroup of patients with good HLA matches (grades A or BU). None of 31 cross-match incompatible platelets provided an adequate increment. An incompatible cross-match result predicts poor responses, but a compatible cross-match does not exclude a poor response. As with red cell antibodies, the sensitivity of the cross-match is
insufficient to detect all alloantibodies. The ability of the cross-match to predict posttransfusion responses may be lower (60% to 80%) in unselected refractory thrombocytopenic patients than in those who are clinically "stable" (80% to 100%), that is, without associated clinical factors. A theoretical limitation of using cross-matched rather than HLA-matched platelets may be the exposure of the patient to a greater number of mismatched HLA antigens to which alloimmunization is possible.

Several methods of cross-matching have been described and found similarly useful to predict the CCI, including solid-phase red cell adherence (SPRCA),77 flow cytometry,78 immunofluorescence, LCT cross-matches, radiolabeled antiglobulin test, complement fixation, platelet serotonin release, platelet factor 3 release, and platelet aggregation.79 Rachel et al.80 found an overall correlation of 97% between SPRCA cross-matching and transfusion outcome. The commercially available SPRCA assay (Capture-P®, IMMUCOR, Norcross, GA) was described by Bock et al.81 SPRCA tests cannot differentiate between alloimmunization to HLA or platelet-specific antigens. Chloroquine or acid stripping of the platelets before SPRCA or platelet cross-match, differential platelet/lymphocyte reactivity, monoclonal antibody-specific immobilization of platelet antigens assay,82 or differential coating of HLA and human platelet antigen (HPA) antigen by enzyme immunoassay83 may be of value in differentiating HLA from HPA antibodies.

We believe that either platelet cross-matching or ordering HLA-matched platelets is an equally appropriate strategy to treat the alloimmunized, refractory patient. The decision regarding which to use should be made initially by each hospital in consultation with its blood supplier and should be determined largely by local factors (eg, Does the hospital perform platelet cross-matching? Does the blood center have a large HLA-typed donor base?) Patients not responding to cross-match–compatible platelets should be given HLA-matched products in case the cross-match is not sufficiently sensitive to detect alloantibodies present. Patients for whom good HLA matches are not available may benefit from the determination of cross-match compatibility with the best HLA-matched products that can be found.

Selection of platelets based on platelet-specific antigen matching. The understanding of the role of platelet-specific antigens in alloimmunization and platelet refractoriness is evolving. Thirteen human platelet antigen (HPA) systems have been described (Table 2). Cases in which poor platelet recoveries are seen after transfusion of HLA-matched and ABO-identical platelets prompt consideration of the presence of platelet-specific alloimmunization.58,84 In multitransfused patients, alloimmunization to platelet-specific antigens is most commonly directed to antigens with phenotypic frequencies below 30%,85,86 whereas alloantibodies directed to the high-incidence antigens are rare.56,87

Although Murphy and Waters88 estimated the frequency of platelet-specific antibodies to be 20% to 25% in multi transfused patients, in the recent TRAP study,50 only 8% of the patients developed antibodies to platelet-specific antigens. Simultaneous alloimmunization to HLA and platelet-specific antigens is not rare. Kickler et al.89 identified antibodies to GPIIb/IIIa in 9 of 293 multitransfused thrombocytopenic patients, and all 9 were also alloimmunized to HLA antigens. In one report, 90% of patients alloimmunized to platelet antigens also had HLA antibodies.90 Between 20% and 25% of patients broadly alloimmunized to HLA antigens also may be alloimmunized to platelet-specific antigens. The contribution of platelet-specific alloimmunization to platelet refractoriness has not been entirely defined. Some studies have found no clear correlation between platelet-specific antibodies and poor responses to platelet transfusion.91,92 Leukoreduction does not appear to affect the rate of alloimmunization to platelet-specific antigens.90

For a patient with a documented platelet-specific alloantibody who is refractory to HLA-matched platelets, the transfusion of platelets lacking the corresponding antigen may be beneficial. Kekomäki et al.93 reported 67 successful transfusions to 6 patients who were simultaneously alloimmunized to HLA and platelet-specific antigens, with platelets matched to both antigen groups. Donor selection based on platelet-specific antigen genotyping by polymerase chain reaction using allele-specific primers to HPA sequences has been reported.94 Empiric transfusion of platelets of known HLA and platelet-specific antigen types may determine which alloantibodies are causing refractoriness in an individual patient.
Table 2. Human Platelet Alloantigens

<table>
<thead>
<tr>
<th>Alloantigen System</th>
<th>Antigen (Alternate Designations)</th>
<th>Frequency*</th>
<th>Glycoprotein</th>
<th>Amino Acid Substitution</th>
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<tbody>
<tr>
<td>HPA-1</td>
<td>HPA-1a (PLA, ZW*)</td>
<td></td>
<td>Ib</td>
<td>Thr145</td>
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<td></td>
<td>HPA-1b (PLA, ZWbl)</td>
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<td>Ib</td>
<td>Met145</td>
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<td></td>
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<td>Ib</td>
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<tr>
<td></td>
<td>HPA-2b (Ko, Sib)</td>
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<td>Ser843</td>
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<td>Arg143</td>
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<td>HPA-3b (Bak*)</td>
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</tr>
<tr>
<td></td>
<td>HPA-11bW (Gro*)</td>
<td>IIIa</td>
<td>His633</td>
<td></td>
</tr>
<tr>
<td>HPA-12</td>
<td>HPA-12a</td>
<td>lIa</td>
<td>Gly15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPA-12bW (Iy*)</td>
<td>lIa</td>
<td>Glu15</td>
<td></td>
</tr>
<tr>
<td>HPA-13</td>
<td>HPA-13a</td>
<td>lIa</td>
<td>Thr799</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPA-13bW (Sit*)</td>
<td>lIa</td>
<td>Met799</td>
<td></td>
</tr>
<tr>
<td>HPA-14</td>
<td>HPA-14a</td>
<td>IIIa</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>HPA-14</td>
<td>HPA-14bW (Os*)</td>
<td>IIIa</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>HPA-14</td>
<td>HPA-14cW (Pa*)</td>
<td>IIIa</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>HPA-14</td>
<td>HPA-14dW (Pa*)</td>
<td>IIIa</td>
<td>Not known</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. These also are known as "platelet-specific antigens." Abbreviations: HPA, human platelet alloantigen; NA, not available.
*Phenotypic frequencies for the Caucasian population only.
†Number not yet assigned.

Autoantibodies, Drug-Induced Antibodies and Passively Acquired Antibodies

The presence of platelet autoantibodies may impair the response to transfused allogeneic platelets; however, decreased platelet survival occurs in only a minority of patients in whom they are detected. Platelet autoantibodies have been reported in acute leukemia, lymphoproliferative disorders, solid tumors, sepsis, cytomegalovirus infections, and hematopoietic stem cell transplantation and its complications. In patients with severe thrombocytopenia and without endogenous platelets available for testing, it may be difficult to prove the existence of autoantibodies, especially at a time when most circulating platelets are previously transfused allogeneic platelets. When strongly suspected clinically, or a previous diagnosis of autoimmune thrombocytopenia already has been made, a trial of high-dose steroids, splenectomy, or intravenous immunoglobulin (IVIG) may be justified.99

Many drugs have been implicated in the development of immune or nonimmune thrombocytopenia. Some of these are likely to be used in patients with
hypo proliferative thrombocytopenia requiring multiple transfusions (e.g., cephalosporins, penicillin, methicillin, TMP-SMX, pentamidine, vancomycin, and amphotericin B). Diagnosis depends on eliciting a temporal relationship of thrombocytopenia and platelet refractoriness with the use of the drug and demonstration of drug-related antibodies. Evaluation for drug-induced antibodies may be warranted in the subset of patients with temporal association to the exposure of an offending drug and the onset of refractoriness. Because of the complexity of the clinical situation, it may not be easy to identify which factors are responsible for refractoriness, and the offending agent should be withdrawn when the diagnosis is strongly suspected, if possible.

The presence of circulating immune complexes and clearance of platelets by the reticuloendothelial system may induce thrombocytopenia. ABO-incompatible plasma in transfused platelets may contribute to formation of immune complexes. The presence of IgG antibodies to plasma proteins was found to increase progressively with platelet transfusions and to correlate with platelet-bound IgG and refractoriness. The degree to which this phenomenon poses a problem in most patients is unknown.

Management When Compatible Platelets Are Unavailable or Ineffective

Alternative strategies for managing thrombocytopenic refractory patients have been reported mainly in small uncontrolled studies or case reports, and interpretation of the benefits of these modalities is difficult. Positive results may be more likely to be reported and published than negative results. No clear-cut recommendations can be made regarding these therapies (Table 3).

Cryopreservation of Autologous Platelets

Platelets collected during recovery of chemotherapy may be frozen in the cryoprotectant dimethyl sulfoxide until needed. Approximately 50% of the platelets are recovered after processing and transfusion. The platelets have normal function and survival. Funke et al reported 78 transfusions of autologous cryopreserved platelets to 8 alloimmunized patients. The in vitro platelet recovery was 85 ± 4%, with a posttransfusion CCI of 11,000. More recently, Torretta et al used single-collection autologous platelets cryopreserved for 25 patients receiving high-dose chemotherapy for breast cancer. Mean platelet recovery was 63% (range, 44% to 81%) after freezing and thawing. Twenty-three patients did not require allogeneic platelet transfusions, and 21 patients had 1-hour CClS greater than 7,500. Platelet size was larger than fresh controls, and there was reduced adenosine diphosphate–induced aggregation, but other agonist responses were adequate. For patients who will go through prolonged periods of thrombocytopenia, several collections may be necessary. Cryopreservation may be used for those alloimmunized patients with few or no compatible donors, but its implementation is difficult, and this practice is not widespread.

Antifibrinolytics

Bleeding was controlled with epsilon-aminocaproic acid (EACA) in 90% (36 of 40) of patients with autoimmune thrombocytopenia or bone marrow failure and alloimmune refractoriness to platelet transfusions. In one randomized study comparing platelet transfusions with and without EACA in 18 thrombocytopenic leukemic patients, there was no significant difference between groups in “major bleeding” or number of platelet transfusions required. However, the authors reported “overall less bleeding” in the treated group. Tranexamic acid was found to reduce hemorrhage in a double-blind trial in thrombocytopenic patients, without an increase in thromboembolic complications. Antifibrinolytic therapy is worth trying for bleeding thrombocytopenic patients without compatible platelets available, or for those who fail to respond to compatible products.

Intravenous Immunoglobulin

Although IVIG therapy may be efficacious for some cases of autoimmune thrombocytopenia, there are conflicting data on the treatment of platelet transfusion refractoriness with IVIG. Most published studies have shown some benefit, but in 3 studies no advantage was noted. Of a total of 66 patients reported, 37 (56%) had improvement in platelet counts posttransfusion, reduction in bleeding, or decreased platelet transfusion requirements. It is possible that successful studies are more likely to be reported. Kickler et al reported a randomized placebo-controlled clinical trial of alloimmunized refractory patients treated with IVIG.
Table 3. Treatment of Platelet Refractoriness

<table>
<thead>
<tr>
<th>Study Reference No.</th>
<th>Number Treated</th>
<th>Responders</th>
<th>Dose/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>8</td>
<td>85% Recovery</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>23</td>
<td>63% Recovery</td>
</tr>
<tr>
<td>17 EACA</td>
<td>17</td>
<td>17</td>
<td>5 g loading, 6 g/d thereafter</td>
</tr>
<tr>
<td>9 EACA</td>
<td>9</td>
<td>9</td>
<td>16-24 g/d</td>
</tr>
<tr>
<td>14 EACA</td>
<td>13</td>
<td>13</td>
<td>8-24 g/d</td>
</tr>
<tr>
<td>9 Platelets + EACA</td>
<td>9</td>
<td>9</td>
<td>100 mg/kg loading dose</td>
</tr>
<tr>
<td>9 Platelets</td>
<td></td>
<td></td>
<td>12-24 g/d thereafter</td>
</tr>
<tr>
<td>109*</td>
<td>6 Tranexamic acid (6 Placebo-no response)</td>
<td>5</td>
<td>6 g/d</td>
</tr>
<tr>
<td>IVIG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>111</td>
<td>3</td>
<td>2</td>
<td>0.4 g/kg/d × 5 d</td>
</tr>
<tr>
<td>112</td>
<td>3</td>
<td>2</td>
<td>0.4 g/kg/d × 5 d</td>
</tr>
<tr>
<td>113</td>
<td>3</td>
<td>3</td>
<td>0.9 g/kg</td>
</tr>
<tr>
<td>114</td>
<td>19</td>
<td>13</td>
<td>0.4 g/kg/d × 5 d followed by 0.8 g/kg/d × 5 d</td>
</tr>
<tr>
<td>116</td>
<td>3</td>
<td>3</td>
<td>2 g/kg/d × 2-5 d</td>
</tr>
<tr>
<td>117</td>
<td>10</td>
<td>6</td>
<td>0.4 g/kg/d × 5 d</td>
</tr>
<tr>
<td>118*</td>
<td>7 (5 Placebo-no response)</td>
<td>5</td>
<td>0.4 g/kg/d × 5 d</td>
</tr>
<tr>
<td>119</td>
<td>2</td>
<td>2</td>
<td>Pt. 1: 0.4 g/kg/d × 5 d</td>
</tr>
<tr>
<td>120</td>
<td>5</td>
<td>0</td>
<td>Pt. 2: 1 g/kg/d × 2 d</td>
</tr>
<tr>
<td>121</td>
<td>7</td>
<td>0</td>
<td>0.4 g/kg/d × 5 d</td>
</tr>
<tr>
<td>122</td>
<td>11</td>
<td>0</td>
<td>0.4-0.6 g/kg/d × 5 d</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>38 (51%)</td>
<td></td>
</tr>
<tr>
<td>Plasma exchange</td>
<td></td>
<td></td>
<td>10 L/d × 2-3 d</td>
</tr>
<tr>
<td>124</td>
<td>18</td>
<td>11 (61%)</td>
<td></td>
</tr>
<tr>
<td>Staphylococcal A protein</td>
<td>6</td>
<td>0.5-2 L plasma processed, 1-4 treatments</td>
<td></td>
</tr>
<tr>
<td>126</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>127</td>
<td>3</td>
<td>0</td>
<td>2 L plasma processed, 4 treatments</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>6 (46%)</td>
<td></td>
</tr>
<tr>
<td>Massive platelet transfusion</td>
<td>130</td>
<td>2</td>
<td>20 Units to adsorb the antibody. Improved increments observed thereafter.</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>131</td>
<td>2</td>
<td>1</td>
<td>12.5 mg/kg/d</td>
</tr>
<tr>
<td>132</td>
<td>1</td>
<td>1</td>
<td>300 mg/d</td>
</tr>
<tr>
<td>133</td>
<td></td>
<td>1</td>
<td>3.3 mg/kg twice daily</td>
</tr>
<tr>
<td>Antithymocyte globulin</td>
<td>135</td>
<td>4</td>
<td>Disappearance of alloantibody</td>
</tr>
<tr>
<td>135</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>HLA stripped platelets</td>
<td>136</td>
<td>1 Patient</td>
<td>73% Recovery in normal subjects; results in patient comparable to HLA-matched</td>
</tr>
<tr>
<td>136</td>
<td>2 Normal subjects</td>
<td>1</td>
<td>GI bleeding stopped</td>
</tr>
<tr>
<td>137</td>
<td>2</td>
<td>1</td>
<td>GI bleeding stopped</td>
</tr>
<tr>
<td>138</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vinblastine-loaded platelets</td>
<td>139</td>
<td>1 (11 courses)</td>
<td>Effect lasted a few days bleeding stopped</td>
</tr>
</tbody>
</table>

*Prospective controlled study.
at 400 mg/kg/d for 5 days. Five of 7 patients receiving IVIG had significant increases in CCI at 1 to 6 hours compared with pretreatment values, but only one had improved platelet survival at 24 hours. Improvement in 1-hour CCI was seen in 4 patients receiving HLA-mismatched platelets. Responses seen with IVIG are usually rapid, ranging from 1 to 9 days, and last for 6 to 8 weeks. One report documented a response lasting over 1 year in a patient receiving chronic platelet support.\textsuperscript{117} Proposed mechanisms include macrophage Fc receptor blockade, platelet coating, and displacement of previously bound antibodies from the platelet surface.\textsuperscript{123} All studies on the treatment of refractoriness are confounded by the spontaneous loss of antibody. Physicians must be mindful that a course of high-dose therapy costs several thousand dollars.

**Other Options**

**Plasma exchange.** Therapeutic plasmapheresis was reported in only 1 case series of 18 alloimmunized patients.\textsuperscript{124} A response was seen in 8 of 13 patients with detectable LCT antibodies at the time of pheresis. The authors concluded that the best responses are seen with 10-liter plasma exchanges performed daily for 3 days. Plasmapheresis also may be considered in patients with autoantibodies or drug-induced thrombocytopenia as a means of removing IgG or immune complexes. This therapy is employed only rarely owing to its limited reported success.

**Anti-D immune globulin.** Heddle et al\textsuperscript{125} reported a randomized trial of weekly intravenous anti-D (20 μg/kg) or placebo given to 43 Rh-positive acute leukemia patients at diagnosis, to prevent the development of refractoriness and to improve posttransfusion platelet increments. No differences were observed between groups, except for an increase in red cell transfusions in the treatment group.

**Immunoadsorption: Staphylococcal Protein A Columns.** There are 2 small case series on the use of extracorporeal immunoadsorption in the treatment of platelet refractoriness. In a study by Christie et al,\textsuperscript{126} 6 of 10 patients refractory to platelet transfusions responded to treatment with staphylococcal protein A columns (PROSORBA, IMRE Corp., Seattle, WA) after failing other immunosuppressive therapy. Responding patients had postransfusion CCIIs at 10 minutes to 2 hours of 48,000 compared with 16,000 pretreatment. Eight of these patients had demonstrable platelet antibodies. Patients received from 1 to 14 treatments, and the total volume of treated plasma ranged from 500 to 2,000 mL per treatment at a rate of 10 to 20 mL/min with apheresis equipment (CS-3000, Baxter, Deerfield, IL) or by an off-line procedure. In another clinical study, Lopez-Plaza et al\textsuperscript{127} found no effect in 3 patients. It has been hypothesized that although staphylococcal protein A binds IgG (except IgG3), the key effect is not immunoadsorption but immunomodulation by induction of antidiotypic antibodies.\textsuperscript{128,129} The usefulness of this expensive approach needs to be confirmed.

**Massive platelet transfusion.** Transfusion of large doses of platelets to immunoadsorb alloantibody or block the phagocytic system has been described in 2 patients.\textsuperscript{130} After 20 pooled platelet units were transfused, the subsequent doses resulted in improved responses and produced a clinically evident effect on hemostasis. Alternatively, continuous platelet transfusion (eg, 1 dose every 4 to 6 hours) has been tried with low success in patients refractory to compatible platelets or for whom such products are unavailable.

**Immunosuppressive therapy.** After 2 to 3 weeks of treatment with 20 mg/kg/d cyclosporin A, refractory dogs had improvements in recovery and survival. Response correlated with drug levels.\textsuperscript{131} Improvement has been reported in 4 patients.\textsuperscript{131-133} Yamamoto et al\textsuperscript{132} reported reduction in LCT antibodies in a 26-year-old patient with aplastic anemia treated with 300 mg cyclosporin A daily for 77 days. PRA decreased from 12 to 3 of 20 cells. Slichter et al\textsuperscript{134} observed reversal of alloimmunization with antithymocyte globulin (ATG) and procarbazine in an animal model.\textsuperscript{134} Transient improvement was shown in one clinical report.\textsuperscript{135}

**HLA Stripped Platelets.** Shanwell et al\textsuperscript{136} treated one HLA-alloimmunized refractory patient with platelets stripped of HLA antigens with citric acid treatment at pH 2.8. Good posttransfusion increments were documented on 2 occasions. Two additional patients have been treated successfully.\textsuperscript{137,138}

**Vinblastine Loaded Platelets.** Wong et al\textsuperscript{139} described the use of vinblastine-loaded platelets (VLP) in a patient with aplastic anemia, thrombocytopenia, and bleeding who developed refractoriness associated with LCT antibody. The infusion of VLP 24 hours before an infusion of pooled platelets resulted in good increments. The effect was main-
tained only for a few days. A total of 11 courses of VLP were infused, until the bleeding symptoms improved. The authors based their study on the successful results obtained by Ahn et al\textsuperscript{10} in patients with idiopathic thrombocytopenia, and hypothesized that VLP produce reticuloendothelial system blockade.

**Thrombopoietin and platelet growth factors.** Hematopoietic growth factors, particularly thrombopoietin (TPO) and interleukin-11 (IL-11), may accelerate endogenous platelet recovery, decreasing dependency on platelet transfusions.\textsuperscript{141} TPO increases the size and number of megakaryocytes, stimulates expression of platelet-specific markers (eg, CD41 and CD61), and sensitizes platelets to the aggregating effects of agonists.\textsuperscript{141-144} Platelets remove TPO from the circulation, and it has been suggested that platelet transfusions may blunt the recovery of megakaryocytes. TPO generates impressive thrombocytosis in mice and humans and modifies thrombocytopenia after chemoradiotherapy in animals.\textsuperscript{141,142} TPO has been available for clinical trials as recombinant human TPO (rHuTPO) or polyethyleneglycol-conjugated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) and has been shown to return platelet counts to normal significantly faster, with higher nadir counts.\textsuperscript{143,144} In patients receiving nonmyeloablative chemotherapy (eg, carboplatin for gynecologic malignancies), platelet counts start to increase after 3 to 4 days of TPO, with a peak effect at 12 to 14 days, with up to a 50% decrease in the need for platelet transfusion.\textsuperscript{141,144} However, neither minimal to no effect in platelet nadirs or time to recovery nor a reduction in the need for transfusion of platelets has been observed after hematopoietic stem cell transplants or myeloablative chemotherapy.\textsuperscript{141} PEG-rHuMGDF has been shown to increase plateletheresis yield 3-fold in stimulated donors.\textsuperscript{141} However, all clinical trials with PEG-rHuMGDF were stopped in 1998 because of development of antibodies to the recombinant molecule that cross-react with endogenous TPO. These antibodies caused thrombocytopenia in almost 10% of normal treated volunteer plateletheresis donors. This problem has not been associated with rHuTPO.\textsuperscript{141,142}

IL-11 works in concert with IL-3 to increase the size, number, and ploidy of megakaryocyte colonies and to increase platelet counts.\textsuperscript{142} It has been reported to prevent severe cumulative thrombocyto-
increase in the platelet count, then testing for LCT antibodies is indicated. If LCT antibodies are detected, then HLA-matched or cross-match-compatible platelets should be transfused. Some of these patients also may need ABO-identical or fresh platelets. Some patients may have rising titers of anti-A or anti-B, if they received ABO-incompatible platelet transfusions earlier in their treatment, and may thereafter require ABO-identical platelets. When only low-grade HLA matches are available (eg, BX, C, or D), cross-match-compatible platelets, if available, may provide better responses. If only platelets that are partially HLA-matched can be collected, it may also prove helpful to cross-match these products. Physicians should remember that HLA class I antigens cause refractoriness in only a minority of patients who are alloimmunized to them.

If there is difficulty finding well-matched platelets for a particular patient, the use of platelets expressing HLA CREGs may benefit some patients. Also, mismatching for antigens not well expressed by platelets (eg, HLA-B12) may prove useful. Patients not responsive to partially matched platelets may be evaluated for alloimmunization to public epitopes (eg, Bw4 or Bw6). If found, patients should be treated with platelets selected for compatibility for the alloantibody detected.

When it is difficult to find well-matched platelets and patients are not responding to transfusions of platelets expressing HLA CREGs, determination of the specificity of the HLA alloantibodies may help guide the selection of products for transfusion in some patients. This strategy has proved particularly useful for patients alloimmunized to HLA-A2.

In patients who continue to be refractory to HLA-matched or cross-match-compatible platelet transfusions, other causes should be suspected. If platelet transfusions well matched for HLA antigens do not result in expected posttransfusion platelet count increments, testing for platelet-specific antibodies should be considered. If such antibodies are present, antigen-negative platelets should be provided, if possible. For individual patients alloimmunized to both HLA and platelet-specific antigens, responsiveness to individual transfusions of known HLA and platelet antigen types may help determine which alloantibody or alloantibodies are principally responsible for refractoriness.

Patients should be monitored every few weeks for the persistence of alloantibody, because many patients lose detectable alloimmunization even with continuing transfusions. Such patients may no longer require HLA-matched or cross-match-compatible platelets, although failure to detect antibodies in vitro does not necessarily mean that there will be no alloantibody-mediated refractoriness in vivo, owing to imperfect test sensitivity.

Patients who are refractory despite the use of the available strategies described above may require additional treatment or preventive strategies, although the efficacy of these modalities is unproven. A course of antifibrinolytic therapy to arrest hemorrhage is relatively safe and inexpensive and may be highly efficacious. IVIG (0.4 g/kg/d x 5 days), although expensive and of unproven efficacy, may result in good platelet recovery in some patients. Other options described above are rarely used owing to their very limited reported success.

The transfusion of leukocyte-reduced cellular components to prevent alloimmunization has emerged as a cornerstone of addressing the problem of platelet transfusion refractoriness. Although this strategy is of proven value, some patients will continue to develop alloimmune-mediated refractoriness to platelet transfusion. The evaluation and management of these patients poses a complicated clinical challenge. The conditions that can contribute to refractoriness have variable significance in different patients, and the available therapeutic options have variable success in different patients. Each refractory patient has a unique constellation of factors that contribute to her or his own insufficient response to platelet transfusions.

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