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Medical and economic implications of strategies to prevent alloimmunization in sickle cell disease

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Abstract

BACKGROUND—The pathogenesis of alloimmunization is not well understood, and initiatives that aim to reduce the incidence of alloimmunization are generally expensive and either ineffective or unproven. In this review, we summarize the current medical literature regarding alloimmunization in the sickle cell disease (SCD) population, with a special focus on the financial implications of different approaches to prevent alloimmunization.

STUDY DESIGN AND METHODS—A review of EMBASE and MEDLINE data from January 2006 through January 2016 was conducted to identify articles relating to complications of SCD. The search was specifically designed to capture articles that evaluated the costs of various strategies to prevent alloimmunization and its sequelae.

RESULTS—Currently, there is no proven, inexpensive way to prevent alloimmunization among individuals with SCD. Serologic matching programs are not uniformly successful in preventing alloimmunization, particularly to Rh antigens, because of the high frequency of variant Rh alleles in the SCD population. A genotypic matching program could offer some cost savings compared to a serologic matching program, but the efficacy of gene matching for the prevention of alloimmunization is largely unproven, and large-scale implementation could be expensive.

CONCLUSIONS—Future reductions in the costs associated with genotype matching could make a large-scale program economically feasible. Novel techniques to identify patients at highest risk for alloimmunization could improve the cost effectiveness of antigen matching programs. A clinical trial comparing the efficacy of serologic matching to genotype matching would be informative.

Sickle cell disease (SCD) is an inherited hemoglobinopathy that is mainly found in individuals of African descent. Although individuals affected by SCD are at high risk of stroke, infection, organ failure, and chronic pain, no organized surveillance mechanisms exist to track health outcomes for patients with SCD in the United States.¹ In addition, patients with SCD are at risk of alloimmunization to minor red blood cell (RBC) antigens as a result of RBC transfusion.^{2–11} Alloimmunization can result in various medical

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CONFLICT OF INTEREST

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complications, ranging from difficulty obtaining medically necessary, compatible RBC transfusions to life-threatening episodes of hemolysis and hemolytic disease of the fetus and newborn (HDFN).^{8,12,13} Consequently, alloimmunization is a medically important concern for patients with SCD and their physicians.

The notion that the incidence of alloimmunization in patients with SCD could be curtailed by the transfusion of RBCs from donors who are serologically matched for at least the C, E, and K antigens has been debated for decades.^{6,14} The basis of a serologic matching program is the difference in Rh and Kell antigen expression patterns among the predominantly Caucasian donor population (which is more likely to express C, E, and K) and the primarily African American SCD population (which is more likely to express c and less likely to express C, E, or K) in the United States. Indeed, some studies have reported reductions in alloimmunization by serologically matching the donor and recipient for these antigens before any antibodies are ever formed.^{5,6} However, other studies have continued to report high rates of alloimmunization despite serologic antigen matching.^{8–11} Although some of these alloimmunization events were likely caused by patients receiving transfusion outside of the study setting at facilities that did not perform serologic antigen matching, it is clear that genetic variations in *RH* create risk for alloimmunization even when serologically matched RBCs are used for transfusion.^{8,13}

Currently, there is interest in evaluating the feasibility of providing RBCs for transfusion that are genotypically matched to the recipient. Early studies have demonstrated the principle that genotype matching between donor and recipient is associated with a very low rate of alloimmunization and improved in vivo survival of transfused RBCs.^{15–17} However, the process of procuring genetically matched units is a departure from decades-old clinical practice that relies on serology; as such, the feasibility of changing this paradigm is uncertain.

The purpose of this article is to review the medical literature pertaining to the incidence and complications of alloimmunization in the SCD population, with an emphasis on the cost effectiveness of various strategies to reduce the incidence of alloimmunization. Specifically, we sought to address the following questions: 1) What are the risk factors for alloimmunization in the SCD population; 2) which adverse events are associated with alloimmunization; 3) what approaches to mitigating the risk of alloimmunization have been evaluated by clinical trials, and have they been shown to be effective; and 4) are the financial costs of strategies to prevent alloimmunization in proportion to the medical benefit provided?

MATERIALS AND METHODS

As a basis for this review, the EMBASE and MEDLINE/ OVID databases were searched independently for articles written in English between January 2006 and January 2016. For the search, the following disease terms were used alone or in combination: “anemia, sickle cell” or “sickle cell disease,” the epidemiology terms “incidence” or “prevalence,” and the clinical term “alloimmuniz*.” In addition, 25 economic terms related to cost, budget, and economic resources were used. Specifically, title/abstract search terms were: “cost,”

“budget,” “expenditure NOT energy,” “resource,” “economic,” “pharmacoeconomic” or “pharmaco economic” or “pharmacoeconomic,” “utilization” or “utilisation,” “price” or “pricing,” “fee,” “economic burden,” and “financ*”; Medical Subject Heading (MeSH) search terms were: “health resources/economics” or “health resources/utilization,” “costs and cost analysis,” “cost of illness,” “economics,” “cost-benefit analysis,” “economics, nursing,” “economics, pharmaceutical,” “economics, hospital,” “economics, medical,” “models, economic,” “value of life,” “fees and charges,” “budgets,” or “resource allocation.” The initial results were obtained by searching disease, epidemiology, clinical, and economic terms. Articles without available abstracts were excluded. Subsequently, additional criteria were applied to focus the results, including: “alloimmunization risk,” “alloimmunization rate,” “antigen testing,” “antigen matching strategies,” “alloimmunization,” “antigens distribution,” “delay for compatibility testing,” “transfusion history,” “blood provision effectiveness,” “prospective matching effectiveness,” “hemolytic transfusion reaction risk,” “hemolytic transfusion reaction events,” “hemolytic transfusion reaction readmission,” “cost for testing,” “cost for different matching strategies,” “cost for providing extended matched blood,” and “hemolytic transfusion related mortality.”

RESULTS

The literature search yielded 168 resources, of which 69 were articles and 99 were conference abstracts. The topics of the articles were primarily related to: the incidence of alloimmunization in patients with SCD, molecular biology of alloimmunization, Rh molecular diversity in various populations, adverse events associated with alloimmunization (particularly delayed hemolytic transfusion reactions [DHTRs]), the effect of serologic matching schemes on the incidence of alloimmunization, the experience of various centers with genotype matching, and economic analysis of matching for minor RBC antigens.

What are the risk factors for alloimmunization in the SCD population?

Most studies report that the alloimmunization rate in the SCD population is approximately 30%, with antibody specificity most commonly reported to an antigen in the Rh or Kell groups.^{8,18–35} Overall, the circumstances that increase the probability of alloimmunization in response to allogeneic RBC transfusion are not well understood.²³ However, studies have suggested that various biologic factors, including patterns of lymphocyte trafficking and genetic heterogeneity between donor and recipient populations, may impact the risk of alloimmunization (Table 1).^{36–45}

In terms of transfusion practice, it is generally accepted that genetic variation between blood donors and transfusion recipients plays an important role in the observed incidence of alloimmunization.^{46–50} For example, Zheng and coworkers reported that patients with SCD residing in the United States had a higher rate of alloimmunization and more alloantibodies per person compared with other countries, such as Brazil, where the genetic composition of blood donors more closely resembles that of transfusion recipients.²⁰ The rate of alloimmunization is believed to be less than 10% in sub-Saharan Africa, where there is significant genetic overlap between donor and recipients.^{32,35,51}

Several research groups have investigated whether transfusions undertaken as part of an RBC exchange program are more (or less) likely to result in alloimmunization compared with simple transfusions.^{52–54} Based on the results from several studies, RBC exchange is associated with a lower risk of alloimmunization per unit transfused compared with simple transfusion, although the pathophysiology underlying this observation is not well understood.^{19,52}

Other hypothesized risk factors for alloimmunization include transfusion with older RBCs, transfusion during an inflammatory episode, greater extent of African ancestry, age of first transfusion, the number of total RBC transfusions, and sex.^{28,55–59}

Which adverse events are associated with alloimmunization?

Most alloimmunized patients with SCD will not have serious complications of alloimmunization.^{14,60,61} However, patients with SCD are at high risk for DHTRs (including life-threatening events).^{12,62–71} For example, Vidler and colleagues reported that almost 8% of SCD patients who received transfusions developed DHTRs over a 5-year period.¹² Several reports show that many episodes of DHTR are initially misdiagnosed as vaso-occlusive pain crisis.^{12,66,67,72} Less commonly, patients with SCD can develop hyperhemolysis syndrome, which is an incompletely understood, life-threatening complication of transfusion characterized by macrophage activation, leading to the destruction of both donor and recipient RBCs (“bystander hemolysis”).^{73–76} The management of severe DHTRs or hyperhemolysis can require admission to a critical care facility and off-label treatment with erythropoietin as well as immunosuppressants, such as intravenous gammaglobulin, rituximab, steroids, and/or eculizumab.^{67,76,77} Although the estimated financial cost of a hospitalization for a DHTR is \$1293.09, the true cost of a hospitalization may be much higher if off-label use of such medication is needed.⁶⁰ In addition, alloimmunization can result in HDFN.^{78–81}

What approaches to mitigating the risk of alloimmunization have been studied, and have they been shown to be effective?

Serologic matching programs, which use antisera to phenotype blood donors and their recipients and then assign phenotypically matched RBCs for transfusion, have generally been viewed as a relatively successful method to prevent alloimmunization and DHTRs.^{53,82,83} Most commonly, these matching programs match either for the C, E, and K antigens or for the C, E, and K antigens in combination with Fy^a, Fy^b, Jk^a, Jk^b, and potentially MNS.^{5,84,85} A report of 105 adult and pediatric patients with SCD reported a 50% reduction in alloimmunization after instituting limited RBC antigen matching (C, E, and K, with the addition of Jk^a, Jk^b, Fy^a, and Fy^b if alloimmunized).⁸⁴ Several other studies have reported significant reductions in alloimmunization as a result of serologic matching programs.^{5,86,87}

However, there are numerous reports of alloimmunization despite serologic matching programs. This “failure” of serologic matching is most commonly associated with transfusion recipients who have variant or partial *RH* alleles,^{88–90} which cannot be reliably identified serologically.^{91–93} In addition, individual patients may receive transfusions at

multiple hospitals, some of which may not provide serologically matched RBCs for transfusion.^{10,11} In a highly influential study, Chou and colleagues reported high rates of alloimmunization among SCD patients despite having received serologically matched RBCs for transfusion.⁸ Eighty-seven percent of individuals in that study had at least one variant Rh allele, and most (64%) of the antibodies formed had Rh specificity.⁸ Similarly, a study of Brazilian patients with SCD did not report a significant reduction in alloimmunization with their limited (Rh and Kell, extended to Kidd and Duffy if alloimmunization occurred) serologic matching program.⁹⁴

Genotyping has several theoretical advantages over serologic typing, including detection of allelic variation, improved accuracy, and the ability to evaluate individuals in the setting of recent transfusion.^{93,95} One large blood center reported that the use of an automated donor-matching program could reduce the probability of exposing a patient with SCD to a potentially alloimmunizing (non-self) RhCE protein by up to 90%.⁹⁶ However, other reports suggest that it may be difficult to recruit sufficient numbers of donors to support patients in need of matched RBCs.^{9,97,98} There is hope that the number of molecular-typed donors could increase in the near future by using new technologies and approaches.⁹⁹

Although there are no large trials that directly compare transfusion of genotype-matched RBCs with serologically matched RBCs, there are published case reports that demonstrate the potential advantages of genotype-matched RBCs.^{16,92,100–102} Costa and coworkers reported improved in vivo survival of transfused RBCs in a cohort of patients with SCD when RBCs were obtained from blood donors who were molecular matches for their recipients.¹⁰⁰ Guelsin and colleagues selected 15 transfusion-dependent patients (10 with SCD, three with myelodysplastic syndromes, and two with β -thalassemia) who received transfusions with extensively genotype-matched RBCs (matched for D, C, c, E, e, K, Fy^a, Fy^b, Jk^a, Jk^b, S, s, Di^a, and Rh variants). After 1 year, the genotype-matching program was credited with improved in vivo survival of transfused RBCs and no additional instances of alloimmunization.¹⁶ Various case reports have described similar outcomes.^{92,101,102}

Are the financial costs of strategies to prevent alloimmunization approaches in proportion to the medical benefit provided?

Two rigorous economic analyses of providing matched RBCs to patients with SCD have been published in the literature. The first compared the cost of providing serologically antigen-matched RBCs in a prophylactic manner (i.e., to prevent alloimmunization) with the cost of providing antigen-matched RBCs only after alloimmunization had already occurred.⁶¹ That analysis was performed with the following input parameters: a one-time, 14-antigen serologic phenotyping of the recipient cost \$364, a unit of RBCs cost \$198.87 with an incremental cost of \$80 per negative antigen, and hospitalization for the treatment of a DHTR cost \$1392.09. In addition, the model assumed that 30% of patients with SCD became alloimmunized over the analysis period (10 or 20 years) and that serologic matching was 85 to 99% effective at preventing alloimmunization events, depending on whether a limited (ABO, D, C, E, K) or extensive (11 antigen match) strategy was employed. The analysis found that prophylactic matching for 11 antigens would cost \$1.86 billion more than matching after a single alloimmunization event but would prevent 2424 instances of

alloimmunization. The authors also reported that prophylactic matching for only C, E, and K would cost \$765 million more than matching after alloimmunization but would prevent 2072 instances of alloimmunization. Overall, the authors concluded that the total lifetime health care cost for a patient with SCD (\$460,000) was similar to the cost to prevent a single instance of alloimmunization using either of the prophylactic matching strategies (range, \$369,482–\$769,284).⁶¹

As mentioned previously, among the major factors that diminish cost effectiveness in antigen-matching protocols is the provision of relatively expensive, matched RBC units to patients who never would have formed an antibody in response to transfusion with standard RBCs. A second cost analysis explored how the cost of providing antigen-matched units would be affected by a hypothetical screening tool to predict patients at risk.⁶⁰ The hypothetical assay was estimated to cost \$1000 and was assumed to be either 100% sensitive and specific (perfectly informed matching) or 40–100% sensitive and specific (imperfectly informed matching). Other costs were assumed to be the same as the previous cost analysis (\$364 for a recipient 14-antigen serologic phenotype and \$198.87 for a unit of RBCs with an \$80 cost supplement for each negative antigen). The approaches considered were prospective matching for all patients, matching only for patients with a history of antibodies, matching based on perfectly informed screening, and matching based on imperfectly informed screening. The authors reported that the cost effectiveness of antigen matching varied based on assay specificity. Relative to prospective matching, an imperfect assay with 75% sensitivity and specificity would save \$108,109 per patient while resulting in an average increase of 0.05 more alloimmunization events per patient over 20 years.⁶⁰ A simpler way to identify patients at risk is to provide transfusion support without matching and then to switch to extended matching when an alloantibody is detected. In most cases, a single alloantibody develops without a clinically significant adverse reaction, allowing an initial alloantibody response to serve in the absence of a hypothetical screening assay.¹⁴

In addition to these two major economic analyses, a conference abstract evaluated the cost implications of a strategy to restrict provision of extensive serologically matched RBCs to a cohort of patients with a history of alloimmunization while providing only ABO and Rh(D)-matched RBCs to a cohort of patients with no history of antibodies. The authors reported that only 26.6% of the patients who initially had no antibodies went on to become alloimmunized as a result of their RBC exchange program. The estimated cost savings of antigen matching only for patients who had antibodies was almost \$1 million.¹⁰³

DISCUSSION

SCD is a complex clinical entity with numerous comorbidities, including stroke, acute chest syndrome, multisystem organ failure, and complications of pregnancy.^{104–110} Although RBC transfusion is one of the best strategies available for the treatment or prevention of many (but not all) of the sequelae of SCD, transfusion is also associated with substantial costs and numerous adverse effects, including iron overload and alloimmunization. Alloimmunization, in turn, poses a risk of inducing life-threatening hemolytic transfusion reactions (6% of DHTRs are reported to be lethal⁷¹), organ damage,⁸¹ chronic pain,⁸¹ diminished survival,^{80,81} and HDFN.² Recently, experts have suggested that providing

genotype-matched RBCs would help to prevent alloimmunization, although it is widely recognized that additional research is needed on this topic.¹¹¹ The literature is clear that serologic antigen typing is not nearly as informative as genotyping, especially in the SCD population, which has a high prevalence of *RH* gene variation.^{16,92,112} Although the provision of genotype-matched RBC units is a scientifically sound and promising approach, there is only limited experience with the practice at this time. A large clinical trial that compares genotype matching versus serologic matching would be informative regarding the implications of a large-scale genotyping program.

Recently published economic analyses have shown that the cost of providing serologically matched RBCs to patients with SCD is high.^{60,61} Even if serologic matching were assumed to be 85 to 99% effective at preventing alloimmunization—a likely overstatement given a recent report of a high incidence of alloimmunization despite serologic matching⁸—it is believed that the incurred cost to prevent even a single alloimmunization event is at least \$369,482 over 10 years.⁶¹ It is important to emphasize that this is an estimate based on economic simulations, not directly measured values. Nonetheless, this figure is driven by two key considerations: 1) that most patients with SCD will not alloimmunize; and 2) that the provision of serologically determined, antigen-negative units is expensive (\$80 per matched antigen, which is a substantial cost relative to the cost of a standard unit of RBCs). The provision of expensive, matched RBCs to patients who will never form an antibody is certainly not economically viable.¹⁴ Although economic analyses reveal that a screening test that is capable of identifying patients who are at risk for developing antibodies could substantially reduce the cost of providing serologically matched RBCs,⁶⁰ at the present time, there is no test available that can reliably predict which individual patients are at higher risk for alloimmunization.

No formal economic analysis has been published regarding the economic feasibility of a genotype-based RBC antigen-matching program. The true economic cost of a unit of RBCs is difficult to quantify, and some factors, such as labor, can be very large compared with the per-unit charge of a blood supplier.¹¹³ However, estimates suggest that the costs of genotyping both donors and recipients could be lower than the costs of phenotyping RBC donors (see Table 2). For example, the estimated cost of obtaining a full RBC antigen genotype on a donor or recipient is approximately \$220, of which approximately \$180 is for the reagents of a commercially available genotyping kit and about \$40 covers the cost of extraction, disposables, and technologist labor. However, the costs of performing genotyping are difficult to estimate because they are highly dependent on the platform that is used for the testing.¹¹⁴ Substantially lower costs (\$47 for reagents, excluding labor) have been reported in high-throughput environments, and in the future, the costs of these reagents may continue to decline.^{114,115} One group that used a high-throughput program to genotype both donors and recipients reported a theoretical cost savings of \$170,800 per month by using molecular methods to match donors and recipients, rather than paying the blood supplier a per-antigen fee.¹¹⁵

The ability to inexpensively test blood donors does not ensure the availability of matched RBC units for transfusion.^{115,116} Due to the high degree of genetic diversity in the African-American population (particularly in the *RH* gene), it is possible that large-scale support of a

genotype-matching program could require increased costs related to donor recruitment and retention. It is highly likely that any large-scale program would need to include large numbers of African-American blood donors. Unfortunately, the historical reluctance of African-American blood donors to participate in US-based blood donation programs further complicates this issue, and novel approaches may be required to improve the recruitment of African-American donors to support a large-scale genotype-based matching program.

One lesson gleaned through worldwide experience with phenotype-matching is the material, negative impact that intercurrent transfusion at hospitals and clinics that do not participate in a matching program can have on an antigen-matching program.^{10,11} In other words, the benefits accrued by years of careful antigen matching can be undone by an occasional transfusion at a hospital that does not provide matched RBCs or as a result of an emergency transfusion that was needed at a time when matched RBCs were not available. Based on the experience with phenotyping, one can imagine that a hospital located in close proximity to another health care center would encounter challenges when unilaterally implementing a genotype-matching program. In addition, even a genotype-matched unit could induce alloimmunization to a mismatched antigen that fell outside of the genotype-based matching program.

From a practical perspective, it is important to note that the process of DNA extraction and molecular testing takes an estimated 8 to 36 hours to complete, even if the equipment needed to perform these tasks is available on site.^{115,116} In addition, despite high concordance between genetic and serologic testing results,¹¹⁶ there is currently only one US Food and Drug Administration-approved genotype test that does not require serologic confirmation. Therefore, the provision of matched RBCs will generally be faster using serologic methods, unless the donor and recipient have previously been genotyped and the recipient has no history of alloimmunization.¹¹⁴ It is hoped that continued easing of regulatory restrictions that currently make genotyping cumbersome—such as adoption of draft US Food and Drug Administration guidance¹¹⁷ allowing labelling of non-ABO/Rh(D) antigen expression based on historical typing—may decrease the cost of providing genotype-matched RBCs in the future.

Collectively, these considerations highlight the need for an inexpensive, reliable test to identify patients who are at risk of forming antibodies to minor RBC antigens as a result of transfusion exposure. A test that could further differentiate between patients who form relatively benign, routine antibodies from patients who would be at high risk for complications of alloimmunization would be even more informative. Such a test, which could be considered a companion diagnostic to a genotype-based matching program, could help to contain costs while improving the availability of genotype-matched units for patients who truly would stand to benefit from their procurement. In the absence of such a test, a reduction in the cost of genotype-matched RBCs is needed to ensure that patients who receive transfusions are protected from alloimmunization.

The medical specialty of transfusion medicine is no stranger to complex questions regarding cost and benefit.^{118–121} In the wake of the acquired immunodeficiency syndrome epidemic in the 1980s, which drove record levels of autologous and directed blood donations, there

has been unyielding pressure to avoid all possible adverse events related to transfusion. Therefore, it is possible that providing genotype-matched RBCs to patients with SCD would be considered reasonable, despite the unproven large-scale efficacy, the significant economic cost, and the large number of individuals that would need to be treated to avert an adverse event. On the other hand, with modern medicine being driven increasingly by concerns about cost and value,^{119,121} it may be that large-scale implementation may not be feasible until 1) a pivotal clinical trial confirms the efficacy of the practice, or 2) the cost of procuring genotype-matched RBCs becomes similar to the cost of providing standard-issue RBCs. Additional studies that further refine the impact of matching programs in terms of quality-adjusted life years would help to further characterize the appropriate response to this important medical problem.¹²⁰

In conclusion, RBC alloimmunization is a significant medical problem for the SCD population. Future work is needed in several areas, including improved methods to identify patients at risk for alloimmunization, a definitive clinical trial to prove the benefits of genotype-matched RBCs compared with serologically matched RBCs, and improved availability of genotype-matched RBCs. The relative value of these potential solutions compared with other areas of unmet medical need is deserving of additional discussion. If genotype-matched RBCs are proven to be of significant benefit and can be procured at a reasonable cost, then they should be made widely available for patients with SCD and for other populations at risk of significant morbidity due to alloimmunization.

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ABBREVIATIONS

DHTR(s)	delayed hemolytic transfusion reaction(s)
HDFN	hemolytic disease of the fetus and newborn
SCD	sickle cell disease

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TABLE 1

Proposed factors influencing patient tendency toward alloimmunization

Age
Degree of genetic diversity between donor and recipient populations
Expression of cellular antigens (e.g., CXCR4, CCR5, TLR2, TLR3, CD40, HLA)
Inflammation
Mechanism of exposure (simple transfusion versus exchange transfusion)
Sex
Total number of RBC transfusions

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TABLE 2

Comparison of benefits and drawbacks of serologic matching versus genetic matching of RBCs for patients with SCD

Variable	Serologic matching	Genotype matching
Effectiveness at preventing alloimmunization	Mixed results reported in the literature	Not tested in any large clinical trials
Factors diminishing effectiveness	Use in donor-recipient combinations with a greater degree of genetic diversity	Patients seeking transfusions at outside hospitals that do not participate in matching
	Patients seeking transfusions at outside hospitals that do not participate in matching	Emergency transfusion with unmatched units
	Emergency transfusion with unmatched units	Lack of sufficient genotype-matched donors requiring substitution of serologically matched or unmatched units for routine transfusions
	Lack of sufficient serologically matched donors	
Cost	Initial patient phenotyping	Initial patient phenotyping
	Initial donor phenotyping	Initial donor phenotyping
	Base cost of RBCs	Base cost of RBCs
	<i>Plus</i>	<i>Plus</i>
	Blood supplier markup for antigen-negative units	Blood supplier markup for genotype-matched unit