



e-Network Forum

CALIFORNIA BLOOD BANK SOCIETY

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Use of phenotype-matched donor RBCs for transfusion of patients with sickle cell anemia

The discussion regarding phenotype matching of donor RBCs for transfusion of Sickle Cell Anemia (SS) patients has generated a diversity of opinions. Here is the question under debate. A recent report by [Vichinsky et al](#) in *Transfusion* Sept., 2001 showed that routine transfusion of phenotype-matched RBCs (matched only for ABO, D, C, E and K) can reduce the risk of new antibody formation in sickle cell anemia patients. What is interesting is that a large percentage of alloimmunizations are preventable by matching for such a limited number of antigens. Other approaches that can reduce risk of alloimmunization have been described, including transfusion of more fully antigen matched RBCs ([Tahhan HR et al.](#), *Transfusion*, 1994) or transfusion of Fy(a-b-) RBCs that are matched for ABO and D antigens ([Sandler SG et al.](#), *Transfusion*, 1997). The e-network was asked to answer the following: **Is prospective RBC phenotype matching of donor RBCs a policy that you currently employ, plan to employ in the near future, or would never employ?** If you currently employ or plan to employ such a policy, to what extent do you (or will you) "match" donor RBCs for sickle cell anemia patients? If you do not plan to employ such a policy, why not? In other words, has the use of RBC phenotype-matched donor RBCs become (or is it soon to be) a community standard for reduction of alloimmunization risk in sickle cell anemia patients?

The following comments were submitted:

1. **A transfusion service in North Carolina** provides blood for approximately 800 sickle cell disease patients. Whenever a SS patient needs transfusion, RBCs are matched for D, C, c, E, e and K. They report using this approach for over 10 years and state that their data show patients who get such partially matched blood have lower rates of alloimmunization. However, they also do their best to avoid giving rr blood to Ro recipients. They try, whenever possible to select Ro RBCs for transfusion of Ro SS patients. Only very rarely do their Ro patients receive rr blood. They feel that this is indicated as a way of maximizing the chance that other antigens will be concordant between donor and recipient.
2. Another transfusion service, **also in North Carolina** reports using leukocyte-reduced, C, E, K phenotype matched RBCs for transfusion of SS patients.
3. **A blood banker in California** commented that his donor center routinely supplies RBC units that are matched for C, E, K, Fya, and S to a medical center that transfuses the great majority of local sickle cell patients. The hospital transfuses most of their non-alloimmunized sickle cell patients with these antigen matched RBCs. In the past, the blood center asked the community hospitals to consider using E-neg, C-neg, and K-neg RBC units (and dropping the requirement for Fya and S negativity for most cases); however, the hospital has demurred. The blood center is able to comply with the "5-antigen-negative approach" for RBC exchange transfusions (where, you can argue that the consequences of an anamnestic delayed transfusion reaction might be severe, given the potentially large amount of newly incompatible RBCs in the patient's system). However, the responding blood banker thinks that this approach is overkill when applied to patients who receive only simple transfusions (for whom, he believes, the literature supports the aforementioned "three-antigen-negative approach" as being very appropriate). The only times when the responding blood banker has put his foot down and argued against shipping RBCs matched for C, E, K, Fya and S, have been in a few emergent cases where not enough "5-antigen-negative" RBC units were immediately available and, upon consulting with the patient's physicians, determined that it would be unacceptable to delay a transfusion merely to screen for those two remaining (Fya and S) antigens.
4. Another blood banker commented that at her facility they transfuse SS patients with RBCs that are phenotype matched for D, C, E, and K, if the patients are part of the pediatric red cell exchange program. Other antigen-negative units are tested and selected if the patient is alloimmunized.
5. **A blood banker at a large community hospital in Los Angeles** (that often treats famous patients) stated that their policy has been to transfuse sickle cell and thalassemia patients with RBC's that are matched for C, E, and K. They have followed this policy for at least 10 years. Very few of

their sickle cell or thalassemia patients have formed antibodies when transfused using this protocol.

6. **A blood banker in New York** wrote that his facility transfuses SS patients with RBCs that are matched for "Rh" and K. In this case matching for Rh means not exposing the patient to Rh antigens they lack, including D, C, c, E and e. Many years ago the responding blood banker published a couple of papers on this subject and those form the basis of their approach: Blumberg N, Peck K, Ross K, Avila E. The immune response to chronic red cell transfusion. *Vox Sanguinis* 44:212-217 (1983). Blumberg N, Ross K, Avila E, Peck K. Should chronic transfusions be matched for antigens other than ABO and Rh(D)? *Vox Sanguinis* 47:205-208 (1984). According to the data, 90% of all sensitizations are to E, e, C, c and K. The sensitization rate is pretty much the same in sickle cell patients, thalassemics, patients with GI bleeds, AML etc. despite what is often written in the literature. The only patients with statistically different allosensitization rates are those with ALL or CLL, who virtually never make new ALLOantibodies (0 of about 300 to date in his experience). By giving D, C, c, E, e and K matched (i.e., avoiding antigens the patient doesn't have rather than matching per se) blood you get rid of 90% or more of the problem. Matching for other "minor" antigens is a waste of time in the responding blood banker's opinion as he reports having never seen someone on D-, C-, c-, E-, e- and K-matched blood make an anti-Fya/b or anti-Jka/b, probably because these antigens are less immunogenic to begin with. Avoiding the additional Th2 "drive" to the recipient's immune system of the more immunogenic Rh and K antigens, and giving leukoreduced blood, which also avoids providing further Th2 "drive" (Th2 cytokines favor antibody formation and allogeneic transfusion favors Th2 cytokine responses), may also be factors. Since about 1/3 of patients who make antibodies make more than one, you probably are avoiding the formation of quite a few other antibodies by removing the possibility of making anti-C, -c, -E, -e, and -K. The responding blood banker also comments that they use this policy for pregnant women, and for patients with sickle cell and thalassemia on chronic transfusion protocols. Most institutions do not transfuse pregnant women with RBCs matched for D, C, c, E, e and K for reasons that are mystifying to the responding blood banker, since the consequences of allosensitization can be fatal for a fetus, but very rarely for a patient with sickle cell disease. He postulates that we should be giving Rh and K matched blood to all women of child bearing age if we are doing it for patients with SS disease, but we don't, and he does not know of anyone else who does either. He discussed these issues some years ago in an editorial in *Transfusion*. Blumberg N. Beyond ABO and D matching: how far and for whom? *Transfusion* 30:482-484 (1990). Very few patients will need c or e negative blood, since the most common phenotypes are r/r, R1/R1/ R1/r and R1/R2, and a lot of the sickle cell patients are Ro/r, so that anti-c and anti-e are even less common. But that is less true of the thalassemics and pregnant women. However, when you start matching for Kidd and Duffy antigens, as some have advocated, you start needing to use frozen blood or extensive searches that greatly increase the cost of this approach.
7. **A blood banker in Pennsylvania** reported that his facility does not perform extended red cell phenotyping for their sickle cell and thalassemia patients. Their SOP calls for matching only ABO and Rh(D), and crossmatching as per any other patient. They see a modest number of sickle cell and thalassemia patients who require chronic red cell transfusions and/or red cell exchanges. The responding blood banker is not convinced that extended phenotyping decreases the incidence of red cell alloantibody formation.
8. **A blood banker in Michigan** reports that they match RBCs for C, D, E, c, e and K when transfusing their sickle/thalassemia patients. They started this approach a year ago for pediatric hypertransfusion patients.
9. At a **university medical center in Minnesota** they report matching RBCs for C, c, D, E, e and K. They also use leukocyte-reduced blood that is <10 days old both for simple transfusions and exchanges. At a nearby large county medical center with more patients, they match for C, c, D, E, e, K and FYa but not FYb.
10. **A blood banker at a county hospital in Los Angeles** (not the Editor's place) said that her facility transfuses SS patients with RBCs that have been matched for C, E and K antigens.
11. **A blood banker in Sacramento** commented that he has never been a fan of phenotypic matching up front for these patients but some of the area hospitals that his center services do this. One does not know which patients will become immunized, and to what, so he would prefer to wait and treat the patient with blood that is matched when there is an identified antibody. This may follow a delayed hemolytic reaction, which is usually asymptomatic, but in his opinion, there is little problem with this. By phenotypic matching up front, added cost is incurred which may never be necessary.
12. **A blood banker in Northern California** commented that her center has been providing hospitals who treat SS patients with C-, E-, K-matched RBCs for about three years now, although Dr. Vichinsky (the first author of the article "Prospective RBC phenotype matching in a stroke-prevention trial in sickle cell anemia: a multicenter transfusion trial") and an individual who practices in her area would like to begin providing extended phenotypic matching for everyone. The responding blood banker's policy has been to provide the limited matching program for any patient with sickle cell disease or thalassemia from the first transfusion and then go to extended matching if they develop an alloantibody. **For patients who are at risk of stroke and are being supported on a chronic red cell exchange program** they attempt to match prospectively for as many antigens as possible but

often have to ignore Fy(b) unless we can confirm it is significant. In order to support this program they have a procedure in the Reference Laboratory that ensures any new donor of African-American descent is automatically phenotyped and entered into their system.

13. Some **additional links** from the e-Network that may be of interest to a discussion of transfusing SS patients can be found at:

- [What is your policy regarding the collection of blood from a person with sickle cell trait, and what is your policy regarding transfusion of such blood?](#)
- [Implications of Sickle Trait Blood for Leukocyte Reduction and Transfusion](#)
- [Should We Irradiate Red Cells Transfused to Patients with Sickle Cell Anemia? **AND**](#)
- a news item: "[Boy Cured of Sickle Cell Anemia \(by Cord Stem Cell Transplant\)](#)"

ADDENDA Oct. 23, 2001

14. The **scientific director of a large blood center in Southern California** wanted to address the use of phenotype-matched donor RBCs from the perspective of a blood supplier. Here is what he had to say: "The practice of using phenotype-(partially) matched RBCs is based on a series of papers showing that sickle cell disease (SCD) patients make fewer alloantibodies using such protocols. The latest such paper is part of the SHOT study published in *Transfusion* (2001;41:1086). I cannot understand why this is a surprise to anyone; if you transfuse blood lacking certain antigens, then patients will not make alloantibodies to the putative antigens. It has also been known for years that patients who make a single antibody are the most likely to make multiple antibodies after further transfusions. Approximately 25% of adults and <10% of children with SCD become alloimmunized. I prefer to switch that statistic around and say that 75% of adults and >90% of children with SCD do not become alloimmunized. Why then should we waste phenotyped units, which are in short supply (and needed for patients who already have alloantibodies) on patients who are never going to make antibodies (i.e., "non-responders"). This is especially true when hematologists demand blood phenotyped beyond Rh and K. I believe that a much better approach is to always phenotype SCD patients before they are transfused, but only give them phenotype-matched blood after they form their first antibody. These are the ones who may make other antibodies (i.e., "responders") (see Ness (*Transfusion* 1994;34:7) and Issitt and Anstee's book (*Applied Blood Group Serology*, 1998, pages 891-2)). About 45% of alloimmunized SCD patients make only one antibody (see *Blood* 1990;76:1431); the first antibody is usually anti-C, -E or -K, so it is easy to find blood for such patients after the antibody is made. Data from Castro et al (*Br J Haematol* 1999;107:2-11) are also pertinent to this: 137 SCD patients became alloimmunized after receiving crossmatched random ABO/Rh(D)-only matched blood. They observed that had the blood been additionally matched for C, c, E, e, K, S, Fya, Fyb, Jka and Jkb, then 37 (27%) of the patients still would have made the following alloantibodies (anti-Jsa, -Cw, -s, -V, -U, -Lua, -Jsb) present in the 137 patients. The only danger of the compromise approach I describe above is that a SCD patient may have a clinically significant DHTR due to the first single antibody. The morbidity of this is unclear from the literature, but Padmanabhan et al (*Blood* 2000;96(11):109b, and *Transfusion* (in Press)) found this to be rare in studying the results of 71 SCD as patients (47% who become alloimmunized). It has also been shown that so-called "hyperhemolysis" often occurs in SCD patients who have received antigen-matched blood (Garratty G. *Transfusion* 1997; 37:357). The SHOT study has some defects as an argument for supporting the use of phenotyped blood. The 61 patients in the transfusion arm of the study were all supposed to receive Rh/K-matched blood, but 80% had been transfused previously and 11 (16%) patients inadvertently received 29 units of unmatched blood. Thus, the latter small group of 11 were the only patients able to make the most commonly found antibodies in SCD (Rh and K), and the most likely "responders" to make other antibodies. It is hard to conceive that HTRs were reduced 90% (2/61 patients) as they did not have a **matched** set of patients receiving non-phenotyped-matched blood to compare with (they only used historical data in the literature for a comparison); one of the 2 HTRs was in a patient who received unmatched blood in error; the other was presumably proven to be due to one or more (data not given) unmatched antigens (Fya, La, S)."

ADDENDA Oct. 29, 2001

15. According to the Lead Consultant in Immunohaematology In the UK, guidelines for pre-transfusion testing have been published by the **British Committee for Standardisation of Haematology** (*Transfusion Medicine*, 1996, 6 273-283) and are applicable to laboratories at all UK hospitals and Blood Centres. These guidelines recommend that all patients with sickle cell disease have their full phenotype tested at diagnosis and are given **blood matched for C, c, D, E, c and K1**. Ro patients are given Ro blood to reduce exposure to Caucasian red cell antigens, and rr blood is used only if Ro blood is unavailable, which happens rarely. No matching is done for Fy, S, s or U unless corresponding antibodies develop. According to the responding immunohematologist, this policy has been in place for over 15 years and they see very few SS patients forming alloantibodies.

ADDENDA Feb. 6, 2005

16. **Editor's Comment:** Readers may find the article by Osby, M & Shulman, I. [Phenotype Matching of Donor Red Blood Cell Units for Nonalloimmunized Sickle Cell Disease Patients: A Survey of 1182](#)

North American Laboratories. Archives of Pathology and Laboratory Medicine: Vol. 129 No. 2, pp. 190–193, of interest in this discussion.

ADDENDA Apr. 4, 2006

17. **A physician who treats adult Sickle Cell Disease patients** reports that one of his patients has developed **anti-Js(a), anti-U, plus an apparent warm autoantibody**. The physician is concerned that should this patient develop any more red cell antibodies, the patient would be "functionally uncrossmatchable". Unfortunately, the patient has **severe, recurrent** sickle cell symptoms that are unresponsive to medical management or to hydroxyurea. Thus, the physician feels compelled to employ a **hypertransfusion regimen** to reduce the patient's disease activity. The inquiring physician usually orders for this patient RBC units that are **negative for U, Js(a), Jk(b), S, K, and E**. Recently, they "found" a unit that was U antigen negative, but the S antigen status was not stated. The clinician opted to transfuse the RBC unit, given what he believes to be the relationship between the S antigen and the absence of the U antigen. The inquiring physician wonders if a red cell donor can be negative for the U antigen, yet be positive for the S antigen. More generally, he wonders **if any cells (or tissues) can express the S antigen and cause alloimmunization to the S antigen, when the donor is U antigen negative**.

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