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The future of red blood cell alloimmunization risk reduction

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In reply

Despite increasing recognition of the rising costs of health care, cost containment within the field of transfusion medicine remains somewhat controversial. We appreciate the thoughtful comments from Webb et al. and Karafin and colleagues in response to our recent analysis of the cost-effectiveness of prospective antigen matching for the chronic transfusion of patients with sickle cell disease (SCD).[1] In addition, we fully agree that our responsibility as clinicians is to our patients and that we should deliberately avoid complacency when it comes to patient safety. Indeed, spending associated with this pursuit is very often appropriate and warranted.

We would like to underscore that cost-effectiveness studies are not designed to identify methods to sacrifice health in an effort to reduce costs. Instead, the intent is to maximize health within the budget available. We do not hope to inform the decision of whether or not to spend the marginal dollar, but rather to inform the decision of how that dollar is best spent. In some cases, cost-savings may occur as a result of providing more efficient care. However, accepting worsened health outcomes is never the intended goal.

There is a growing consensus that cost-effectiveness studies are as appropriate in the field of transfusion medicine as in other areas of medicine and health care delivery.[2,3] While across all patients, blood transfusion accounts for a relatively small portion of all hospital costs, transfusion may be responsible for significant spending in select patient populations.[3] In the United States, the annual cost of red blood cell (RBC) transfusions is estimated to be greater than $14 billion,[3] and these costs appear to be increasing. RBCs are also a limited resource, and antigen-matched RBCs are even more scarce. These resource limitations, in addition to financial constraints, make cost-effectiveness studies warranted and even *necessary*.

Webb et al note that the recently published NIH guidelines recommend matching for C, E, and K1 antigens. However, this recommendation was based on “low quality” evidence; the guideline authors emphasized this by stating “minimal evidence is available to support a particular method to reduce or prevent side effects from RBC transfusion … The systematic review did not identify comparative effectiveness studies that explored different cross-

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matching approaches."[4] Furthermore, Chou and colleagues recently showed that there can even be unanticipated alloimmunization with "matched" blood,[5] which supports numerous other studies showing that limited matching for C, E, and K1 only reduces ˜85% of alloimmunization events.[6] Webb et al also suggest our model will limit chronic transfusions. However, our model only evaluates antigen matching and does not limit chronic transfusion therapy; thus, it does not impact the incidence of acute chest crises or vasoocclusive events.

Webb et al state that we do not account for substantial non-monetary impacts of alloimmunization. However, primary alloimmunization events are generally clinically silent because of the time course of antibody development following transfusion.[7] Only on very rare occasions, primary alloimmunization may be associated with clinical hemolysis.[8] For the rare, clinically significant cases of alloimmunization, we incorporated the average cost of these hospitalizations. Non-monetary costs are often difficult to define, and in this model, we focused on the perspective of a hospital and included direct medical costs only. This meant that while we did not account for the broader non-monetary benefits Webb et al mention, such as the potential for improved "patient experience" from prospective matching, we also did not account for broader non-monetary costs associated with prospective matching, including the potential for increased delays in service or decreased hospital efficiency. Furthermore, Webb et al note that we assume availability of matched units. Indeed, we make this simplifying assumption, and detail it in our discussion. Prophylactic matching prior to alloimmunization, as we note, only further decreases the total availability of RBC units.

Webb et al suggest that a cost-utility model should be used to translate the effects of matching into quality-adjusted life years (QALYs). While cost-utility models are widely utilized in economic evaluations, there are few widely accepted standards for how to translate an alloimmunization event into a QALY. Furthermore, because there is such wide variation in the impact of alloimmunization and many of these events are not clinically significant, attempting to define QALY impacts may be a misguided pursuit.

As Karafin and colleagues note, we, as a transfusion medicine community, spend substantial amounts on policies and programs to reduce transfusion-transmitted diseases. These costs are often mandated by the FDA and are associated with blood safety initiatives of proven efficacy. In this study, however, we focused on prophylactic antigen matching, which is not mandated by a regulatory body, is expensive and is not clearly efficacious as it is currently performed.

Within the context of preventing alloimmunization, Karafin and colleagues encourage us to rely on historically matched regular donors to providing antigen-matched units to all transfused patients. This practice is permitted with the 29th edition of AABB Standards (5.8.4 and 5.13) and would be ideal. However, reliance on these units alone is simply not possible due to current supply constraints. Even if matched RBCs were always available, providing selected RBCs before alloimmunization would immediately increase turnaround time for transfusion recipients and increase expenses, without providing substantial clinical benefit.

Karafin and colleagues also suggest that we prioritize the improvement and expansion of antigen matching methods rather than making the best of our somewhat constrained reality. We fully agree that molecular genotyping is becoming less expensive and more wide-spread and that this could eventually lead to cheaper testing and risk reduction. However, in our currently resource-constrained context, efficient and widespread testing methods are unlikely to resolve the underlying scarcity of matched blood.

The model we have described compared the health and financial implications of four antigen matching strategies for chronically transfused patients with SCD. While we incorporated costs and consequences associated with alloimmunization, the true adverse consequences of making a single RBC antibody may vary and may not be entirely known. Our goal was to focus on strategies that could plausibly be implemented today, rather than to consider hypothetical scenarios based on possible future technologic developments. However, we did publish a subsequent study on the value of a potential (likely molecular) assay to further refine and guide antigen matching strategies to avoid alloimmunization.[9]

We believe that transfusion patients should receive the safest possible transfusion. What we have attempted to do in our analysis, however, is simply to ground this possibility in current reality.

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