HHS Public Access

Author manuscript

JAMA. Author manuscript; available in PMC 2017 August 10.

Published in final edited form as:

JAMA. 2015 October 20; 314(15): 1557–1558. doi:10.1001/jama.2015.10890.

Red Cell Transfusion: Precision versus Imprecision Medicine

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In the early 20th century discovery of blood groups led to the first example of "precision medicine."(1) By matching blood donors with their recipients, personalized therapy improved transfusion safety.(2) In the 1960's, NIH established a partitioned data set on a mainframe computer with 2700 blood donors phenotyped by serology for 20 red cell antigens. Combining mid-20th century genetic typing technology with the emerging field of informatics served to enhance donor-recipient compatibility and red cell inventory management. "Extended typing" simplified transfusion for patients with red cell antibodies, reduced the risk of future red cell alloimmunization, and became standard management for sickle cell patients. However most hospitals faced with transfusion compatibility problems still looked for antigen-negative red cell units by screening local inventories with inefficient, labor-intensive serologic assays.

Fast forward to the 21st century and the emergence of initiatives on precision medicine. Inexpensive molecular typing paired with powerful bioinformatics has enabled mass-scale red cell genotyping. The genes encoding the significant blood group antigens have been cloned. DNA sequence differences have been correlated with red cell antigen expression. Rapid screening for nucleotide polymorphisms in blood group coding sequences has been accomplished. A new generation of automated DNA analyzers will supplement and could replace serology methods for selecting the most suitable red cell units for patients with multiple alloantibodies. Web-based data storage and analytics are revolutionizing the provision of antigen-negative blood with an efficiency scarcely conceived of just a decade ago. Although currently not practical, providing extended antigen matching by molecular techniques to all patients should improve typing accuracy and reduce alloimmunization.(3) A broader genetic database is important for locating uncommon red cell units, those negative for common antigens or combinations of antigens, and is particularly valuable for countries such as the US with genetically diverse, multiethnic populations.

In a pilot program, a regional blood center genotyped 43,066 donors for 42 clinically relevant antigens in a four-year period.(3) More than 99% of patient orders for red cell units

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The views expressed are those of the authors and do not necessarily represent the view of the National Institutes of Health, the Department of Health and Human Services, or the U.S. Federal Government.

were filled. Now in routine use, this program has successfully filled some 14 thousand requests by using genotype data. A web-based interface allows community hospitals to search local inventories for the most suitable units via an antigen query portal. This example of precision medicine, largely invisible to the practicing physician, promises to transform the way compatible blood is supplied and provide better, more efficient care. Start-up costs, legacy information systems, and the need for FDA-licensed molecular assays have delayed widespread adoption of this approach in the US. However blood services in several European countries are introducing comparable systems at this writing.

In contrast to the precision of genotyping and personalized red cell matching, the decision to transfuse red cell units has become less precise. Current transfusion guidelines rely primarily upon a single hemoglobin concentration as a "transfusion trigger."(4) It seems counterintuitive to believe that one size would fit all patients. Clinical circumstances, co-morbidities, and genetic differences can influence the need for red cell transfusion. However practice guidelines are marginalizing these factors in transfusion decisions and defaulting to a single numerical trigger. Protocol-driven therapy designed for the average patient may benefit the majority, yet still prove suboptimal or even hazardous for a substantial minority. Indiscriminate reliance on fixed targets and rigid protocols falls into the category of "imprecision medicine."

Using hemoglobin concentration to determine the need for red cell transfusion is a time-honored and well-reasoned concept, but the original recommendations from 1942 have regularly been misunderstood and misused. The oft-cited "10/30 rule" (hemoglobin/hematocrit) was less a rule than a proposal: to include hemoglobin as one of several perioperative measures to improve care for poor risk surgical patients. That guidance was prudent for the intended patients and the era, but was never meant to be generalized as the sole determinant of transfusion. The term "transfusion trigger" derives from a retrospective analysis of 535,031 surgical patients that described several factors associated with transfusion.(5) Hemoglobin concentration and decline in hemoglobin concentration were important considerations, as were volume of blood lost and change in vital signs. Somehow the notion that whenever the hemoglobin concentration falls to 10 g/dL or below patients should receive blood became enshrined in medical teachings.

Early practice guidelines for red cell transfusion that relied upon expert opinion (read personal experience), were considered too arbitrary and casual. To provide a credible evidence base, several prospective randomized controlled trials (RCTs) have been completed and published.(6) Their common design involves randomizing patients to receive transfusions at one of two predetermined hemoglobin concentrations. The lower concentration is commonly defined as the "restrictive" and the higher concentration as the "liberal" threshold. Most, but not all of these RCTs have reported that the restrictive arm is at least as safe and effective as the liberal arm and more cost-effective. However concerns have been raised about generalizing these conclusions, particularly for patients with cardiovascular disease, where higher mortality has been observed with a restrictive-threshold and no added benefit with respect to postoperative morbidity or total costs.(6)

RCTs are appropriately considered the “gold standard” for evidence-based medicine, but not all trials are created equal. The design weaknesses of the transfusion trials have been described. (7) The hemoglobin concentrations selected are relatively arbitrary. Strict adherence to randomization based on hemoglobin concentration results in withholding transfusion from some patients in the restrictive arm who would likely benefit, and transfusing some patients in the liberal arm who have no other apparent indication. Comparing the two groups becomes problematic. Trials of this design determine which of the two strategies should not be used, but not which strategy should be used. The superior trial arm could still be inferior to usual titrated care in which all available physiologic and clinical measures supplement the hemoglobin determination in the decision to transfuse. No RCT has included a “usual care” arm. Finally, most studies report substantial numbers of patient exclusions, patients not consented, and noncompliant transfusions, which raises further questions about acceptability and generalizability of the results. Perhaps for these reasons, and not just for lack of education, many physicians seem reluctant to adopt restrictive transfusion practice guidelines.(8)

Whereas precision medicine is commonly equated with genomic medicine, other technical advances, including non-invasive monitoring, imaging, and applied bioinformatics facilitate more personalized medical management as well. Such new technologies could be developed and applied to the decision to transfuse. Conclusions from the existing RCTs are cited as evidence that protocol-based care for transfusion is demonstrably safer than personalized care and that “restrictive” protocols are at least as safe and effective as titrated care. Neither hypothesis has been tested. In addition to designing new RCTs incorporating usual care or comparative effectiveness studies limited to comparing hemoglobin-based triggers, added effort should be devoted to developing sensitive measures of tissue hypoxia and other appropriate, physiologically-relevant parameters. Integrating personalized physiological and clinical factors that provide objective bases for initiating, continuing, or discontinuing red cell transfusion into RCTs could better inform the decision to transfuse. Current transfusion guidelines, though well-intentioned are admittedly deficient.(4) The objectives of reducing exposure to allogeneic blood and conserving a precious resource however commendable fall short of the ultimate goal – improving patient outcomes. Precision in the personalized matching of red cell units is gradually being embraced. A similar degree of precision should apply to its administration.

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