Editorial

Thresholds, triggers or requirements—time to look beyond the transfusion trials

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The conventional medical approach consists of making a diagnosis and prescribing evidence-based treatments to address the disease or condition. For pneumococcal pneumonia, penicillin G at doses 20–24 million units/day has been recommended after verification of no resistance (1). The therapy is introduced once clinical symptoms of lung infection are confirmed with the bacteriology results. Several clinical trials, investigating the use of this therapy at different febrile levels or in presence of other clinical findings are largely absent since there is a defined disease and a defined therapy. Not so when it comes to therapeutic blood transfusions since a defined disease is absent and generally, only a single laboratory value is used for initiation of this treatment.

While data from observational studies on harms of allogeneic blood transfusion had been accumulating for some time (2), the Transfusion Requirements in Critical Care (TRICC) trial has been credited with being the first major trial to show that in critically ill patients (arguably the most vulnerable and sick patients encountered in medicine), using a restrictive transfusion strategy is as effective and possibly even superior to a liberal transfusion strategy (3). Nonetheless, the authors raised some concerns on whether their conclusion could be applied in patients with acute myocardial infarction and unstable angina; patients who are purported to have more limited reserve capacity and higher susceptibility to hypoxia in context of low hemoglobin levels (3). Since TRICC trial, the findings have been largely corroborated by several other randomized trials in various patient populations and the consensus remains that allogeneic blood transfusions can be safely avoided in most patients at hemoglobin level above 7–8 g/dL (4).

It is now 17 years since the publication of the first TRICC trial and we are presented with another well-designed and large randomized controlled trial. Mazer *et al.* have undertaken a colossal endeavor enrolling 5,243 adult patients undergoing cardiac surgery in 73 centers across 19 countries in Transfusion Requirements in Cardiac Surgery III (TRICS-III) trial (5). They randomized the patients to a restrictive transfusion strategy (transfusion when hemoglobin <7.5 g/dL during or after surgery) or a liberal transfusion strategy (based on a hemoglobin threshold of <9.5 g/dL in the operating room or post-surgical critical care unit or <8.5 g/dL on the ward). The primary outcome was a composite of all-cause mortality, myocardial infarction, stroke or renal failure anytime during hospitalization and up to 28 days after the surgery (5).

The large sample size of the study was calculated to allow a non-inferiority margin of 3% risk difference between the study arms with power of 90%. In effect, the composite outcome occurred in 11.4% of the patients randomized to

restrictive arm versus 12.5% in those assigned to the liberal arm, amounting to an absolute risk difference of 1.11% (95% CI, 0.72–2.93) and a nonsignificant odds ratio of 0.90 favoring the restrictive arm. These results unequivocally support the notion that restrictive transfusion strategy is not inferior to liberal transfusion strategy in terms of the studied outcomes (5). With the evidence so strong and consistent with a host of prior studies, can we close this chapter and move on?

Although the TRICC trial was credited as a pioneer in the battle between liberal and conservative (restrictive) transfusion strategy camps, it was not the first study to address the impact of lowering the hemoglobin triggers (better referred to as "thresholds") for transfusion (3,6). After decades (and so many other studies) it might help to take a step back and reconsider the impetus to design that study and those that followed. As stated by Hebert *et al.* in their landmark paper, the key issue was the opposing views on the risks of anemia and benefits of allogeneic blood transfusion (3). This view is essentially *de facto* acceptance of red cell transfusion as the only viable and possibly the best treatment for falling hematocrit or hemoglobin levels. When we limit ourselves to the dichotomy of accepting anemia or ordering blood, we are bound to repeat the same futile cycle over and over.

In the infamous Tuskegee study, a proven treatment was knowingly withheld from patients under a scheme to "study" the natural course of syphilis. Similarly, in the New Zealand Cervical Cancer Experiment (now widely known as the "Unfortunate Experiment"), women diagnosed with carcinoma *in situ* of cervix were deprived of appropriate treatment as part of the study (7). Both cases later faced widespread outcry and these and other atrocious cases of human experimentation without proper consideration of rights of the patients led to the emergence of the Declaration of Helsinki, laying out the foundation for ethical treatment of subjects in research studies. In our opinion, withholding treatment until late symptoms or signs occur is the corollary with anemia. Therapy is withheld until the transfusion trigger is met depriving patients from early intervention and possibly a cure.

We should be very careful in not drawing parallels and there really is no parallel here as the transfusion trials have all abided by the applicable ethical standards and were conducted under auspice of ethics committees. Nonetheless, while we are all appalled by withholding the proper treatment from patients in the Tuskegee or New Zealand studies, we seem to be much less disturbed by the apparent failure to provide proven treatments to patients enrolled in transfusion trials (and by extension, vast majority of patients who go through our hospitals for various reasons while struggling with anemia).

The Figure 1 in the paper of the study by Mazer *et al.* depicts the changes of hemoglobin level in the study arms during the hospital stay and it is quite telling (5). Both study arms enter the operating room with similar average hemoglobin levels of about 13 g/dL but their hemoglobin level take a dive down to below 9 g/dL during surgery. The patients leave the operating room and enter the ICU with average hemoglobin levels around 9.5 g/dL in restrictive arm and around 10.5 g/dL in the liberal arm (in part due to allogeneic blood transfusions which are given to most of the patients regardless of the study arm), and then for the next few days undergo another drop in hemoglobin levels down to around 9 g/dL in restrictive arm and around 10 g/dL in liberal arm. Most startlingly, the patients' average hemoglobin concentrations hover around these same levels for the rest of their stay and never fully recover. Other trials have very similar figures showing drastic initial drops in hemoglobin levels during surgery and persistence of anemia throughout the hospital stay (8).

In our opinion, this observation raises some questions that demand answers. Of high interest for all these trials is the question of why patients end up with these low hemoglobin concentrations? Is it because of the presence of significant anemia that is untreated prior to surgery? Is it avoidance or lack of incorporating the available guidelines on blood conservation in cardiac surgery (9,10)? Maybe it is surgical blood loss due to somewhat less vigilant surgical technique that can easily be rectified with a tincture of time and attentiveness? Or perhaps, it is due to allowing for post-operative blood loss, thinking that it can always be rectified with allogeneic transfusions. An average hemoglobin drop of 4 g/dL during cardiac surgery can be explained to some extent by the impact of the cardiopulmonary bypass and delusional effect of fluids given intraoperatively but part of this drop is undoubtedly related to surgical blood loss. Patient's own fresh whole blood (not processed, stored and possibly aged red blood cells of donors) finds its way into surgical sponges and suction canisters and from there is discarded as waste. There are effective ways to reduce this wastage, from optimization of the hemostasis to use of autotransfusion techniques (cell recovery equipment) (11). Fortunately over 90% of the patients in the TRICS-III trial received tranexamic acid during surgery—an effective, safe and low-cost hemostatic agent, but no information on other

intraoperative blood conservation modalities is provided (5). As noted earlier, guidelines including those from the Society for Thoracic Surgery (STS) and European Association for Cardio-Thoracic Surgery (EACTS) are available that can help mitigate these issues and reduce the hemoglobin drop in patients undergoing cardiac surgery (9,10).

While we understand that surgical blood loss might be inevitable in a surgery as extensive as open heart surgery, we cannot understand what appears to be acceptance of anemia during the postoperative period. In the TRICS-III trial and similar to most of patients who undergo cardiac surgery (5), the vast majority of the patients are discharged well within a week of the surgery and while this might not offer enough time to see the result of proper treatment of anemia emerging in its full potential, some improvements in hemoglobin level is still achievable. Furthermore, for the patients staying in hospital beyond a week, the observed absence of restoration of hemoglobin level is disappointing. Again, it is understandable that most of these patients experienced complications and other issues that delayed their discharge, but in our opinion and when the negative consequences of anemia and its impact on worsening of outcomes is considered (2), we should be even more motivated to properly treat anemia in these patients (12). Hence we ask our colleagues, are we leaving a treatable yet potentially hazardous condition in our patients untreated?

In the TRICC trial and the studies that followed and compared liberal versus restrictive transfusion strategies, mortality assumed the primary endpoint role (or was part of the composite primary endpoint as in the TRICS-III trial) (5) but measures of improved health were usually absent or estimated through other surrogate measure such as lower ventilator days or reduction in acute kidney injury. Direct improvement in health that is tightly related to improved oxygen delivery and utilization and physiologic responses to treatment of anemia, were absent or at best, obscured. It should be remembered that while mortality rate is a very important endpoint and it is often required to be included in these types of trials, its low occurrence across many patient populations makes it an inadequate endpoint that can easily miss significant variations in health and quality of life of the patients (13).

Interpreting the results of previously conducted trials have yielded different opinions. Many have concluded that there is no difference between the thresholds but hidden within the data are some surprises that may alert the reader to consider a different approach to transfusing their patients. One example is the Transfusion Requirements in Septic Shock (TRISS) trial in which there was no difference in mortality or few other surrogate measures of health (8). Of interest is the occurrence of serious adverse reaction to transfusion which was reported in 1 out of 489 patients randomized to liberal transfusion strategy versus none in 488 patients in the restrictive strategy. Such low event rates will certainly yield a nonsignificant P value, but this event rate is still almost 10-times higher than reported incidence of serious transfusion reaction (14).

Prior to the TRICS-III study, Transfusion Indication Threshold Reduction (TITRe2) trial showed no difference between the liberal and the restrictive groups in terms of serious infectious or ischemic events within three months, except for a statistically significant increase in mortality rates (4.2% in restrictive *vs.* 2.6% in liberal transfusion arm) (15). Although no sound physiologic explanation was offered by the investigators as to why this increase only occurred (or became statistically detectable) at 90 days but not earlier, a closer examination of the mortality causes may reveal that the deaths may have nothing to do with restrictive transfusions (data available in the Supplementary Appendix of the manuscript accessible online)*. In addition, the liberal and restrictive transfusion groups both received substantial amounts of blood transfused whilst all were revascularized and their coronary disease was surgically treated, suggesting a significant bias toward liberal use of blood components regardless of study arm allocation (15). This recurring theme is seen in most other transfusion trials in which both study arms receive large amounts of blood and TRICS-III trial is no exception (5).

The investigators of these complex and demanding trials should be commended for their efforts regardless of the results. Each one of these trials desires to claim "definitiveness" yet it seems that none are, as we are still in search of answers. Rushing to change the clinical practices based on the latest published randomized controlled trial is generally discouraged unless a series of trials provide consistent and confirmatory results. In this arena of liberal versus restrictive transfusion threshold trials, we have a large number of reports confirming either superiority

* Murphy *et al.* N Engl J Med. 2015 Mar 12;372(11):997-1008. Supplementary Appendix available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1403612/suppl_file/nejmoa1403612_appendix.pdf (Accessed Dec 28, 2017)

or non-inferiority of restrictive approach. Accordingly, "ditching" the liberal transfusion strategies in favor of more restrictive strategies looks like a no brainer.

Does this then answer the question of when to transfuse? We may conclude that we should transfuse patients at hemoglobin level X but do we know who actually benefits form a red cell transfusion? One can simply see that after the enormous efforts and very high costs of these trials, we are still left without clear answers for the above questions that are faced by every clinician at hospitals every day, since the outcome of mortality which is the focus of many of these trials does not confer improved health. More perplexing is the fact that some patients in liberal arms might not have been transfused while many patients in restrictive arm are transfused. Returning to the pneumonia paradigm, are these randomized trials of liberal *vs.* restrictive transfusion dose escalation studies in reverse? Or are they essentially safety trials for hemoglobin threshold? Adding confusion to the already unscientific and haphazard practice of transfusion (evident from the highly variable transfusion rates for otherwise similar patients) (16) reinforces the practice of conviction that is abundant in this field. The confusion leads to the one-size-fits-all scenario where the hemoglobin level becomes the reason and indication (and even endpoint) for transfusion regardless of the clinical condition of the patient. Not to mention that the supposedly almighty hemoglobin level is just a laboratory value that is prone to measurement errors as much as 1 g/dL (17). Not every patient "requires" a blood transfusion at hemoglobin level of 7 g/dL, while some may see benefits from a transfusion at a higher hemoglobin level. Inherent in all of this is the notion that it is a binary event—either transfusion or no transfusion. When did medicine become so indisputable to the point of forgetting about other treatment modalities and preventive strategies?

Despite all the issues and shortcomings that affect transfusion trials in general, the TRICS-III trial has many strong points beyond its large patient size. It is somewhat unique since it was conducted across multiple hospitals in different countries. The trial included sicker patients and more closely resembled the real life practice of medicine (as opposed to ideal and "sanitized" patient populations studied in some trials). It accounted for all red blood cell transfusions occurring during the course of care in the operating room, ICU and ward except prior to randomization, and it showed reduction in transfusion as a group and per patient (something that can be important considering the dose-dependent side effects of transfusion).

This brings us back to the question of what it is that we are treating—a hemoglobin number or a medical condition? None of the randomized trials discussed here or others set the stage by identifying a disease to be treated, but instead focus on addressing the adverse events and risks of allogeneic blood transfusion. When reverting back to the basis of medical intervention (disease management), proper diagnosis is required, seeking the appropriate treatment for individual patient rather than offering just one treatment for all (since many treatment modalities are available for most diseases) and making a concerted effort to introduce modes of prevention (which is supposed to be better than treatment). Anemia—especially in this population—has been largely ignored and is generally only addressed if a certain hemoglobin threshold is reached for a transfusion decision (13). No attempt at identifying the pathology of anemia, i.e., iron deficiency, anemia of inflammation or combination of nutritional and those above is deemed necessary since the only response is often to ignore and wait and then quickly raise the hemoglobin level with some allogeneic blood and expect improvement in survival (and not necessarily improvement of patients' health or cure of the disease). A transient and symptomatic remedy—the best that can be expected with transfusion—replaces any and all of the management strategies for this widespread disease (18).

The Institute for Healthcare Improvement (IHI) Triple Aim initiative seeks better care for individual, better health for populations and lower per capita cost of health care (19). Going by this model, we believe that we should turn our attention to better management and expect better outcomes with more appropriate resource utilization for cardiac surgery patients. However, the Triple Aims will not be achievable if we continue to be myopic and see transfusion as the only modality for treatment of anemia and continue counting the dead or alive as the main outcome of interest. If prevention, early detection, proper diagnosis and best therapeutic choices is how we address all other diseases of medical conditions, why do we continue to fail our patients when it comes to anemia?

The average preoperative hemoglobin level of 13 g/dL in the patients participating in the study by Mazer *et al.* means that many entered the operative room to undergo a high-risk, high-blood-loss procedure while already anemic. Given the risks of anemia and transfusion, we have argued in past that anemia should be considered a contraindication for elective surgery and procedure should be postponed until anemia is properly managed. Algorithms have been

developed and proposed to detect and manage anemia in the preoperative period (stating with screening for anemia as early as 4 weeks ahead of surgery to allow enough time for proper management of anemia if present) (20,21). Once anemia is diagnosed and depending on the etiologies, various pharmacologic interventions including iron (preferably newer intravenous formulations for faster and more effective restoration of iron stores) and erythropoiesis stimulating agents are available to improve hemoglobin level (22). Finally, one should remember that the fight against anemia does not end with the surgery. As the data from Mazer *et al.* and other studies show, low hemoglobin levels persist in the post-operative period and so does our responsibility to diagnose and treat anemia (including new-onset hospital acquired anemia) in this period (23).

In their conclusions, Mazer *et al.* allude to the existence of treatment modalities other than transfusion but revert to suggest that more trials with different thresholds might be suitable to conduct. We beg to differ as the answer we seek does not come from trials of various transfusion strategies. It is time to examine transfusion versus proper management of anemia in a randomized controlled trial that is structured to not only look at survival or other severely morbid events but improvement in the patients' health and quality of life.

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Footnote

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