HOSPITAL CHRONICLES 2020, 15(1): 7–17

CRITICAL REVIEW

Red Blood Cell Unit Utilization in the ICU: Evidence and Confidence

Dimitrios Zervakis, MD[1], Stylianos Saridakis, MD[2]

[1]Intensive Care Clinic
[2]Blood Bank, Evangelismos Hospital, Athens, Greece

KEY WORDS: *red blood cell units, transfusion strategy, intensive care unit*

Abbreviation List:
APACHE: Acute Physiology and Chronic Health Evaluation
BSH: British Society of Hematology
ED: Emergency Department
ICU: Intensive Care Unit
ITT: Intention to Treat principle
POIP: Phases of Illness Paradigm
PP: Per Protocol (data analysis)
MINT: Myocardial Ischemia and Transfusion
MODS: Multiple Organ Dysfunction Syndrome
TITRe 2: Transfusion Indication Threshold Reduction
TRACS: Transfusion Requirements After Cardiac Surgery
TRICS-III: Transfusion Requirement in Cardiac Surgery
TRIGGER: Transfusion in Gastrointestinal bleeding trial (confirmed by main author)
TRICC: Transfusion Requirements in Critical Care
TRIPICU: Transfusion Requirements in Pediatric Intensive Care Unit
TRISS: Transfusion Requirements in Septic Shock

Correspondence to:
Dimitrios Zervakis, MD
Tel.: 2132041913
Fax: 2132041389
E-mail: dzervakis@hotmail.com

Manuscript received January 23, 2017;
Revised manuscript received June 23, 2018;
Accepted May 25, 2020

ABSTRACT

BACKGROUND: Anemia is a universal finding among ICU patients. It extends below traditionally accepted lower accepted limits for common ward patients and is only moderately counterbalanced with transfusions. To save red blood cell units, the notion of low threshold was introduced. Beginning from the ICU patient population, the threshold strategy at the level of 7 g/dl is encouraged now to be generally investigated and applied.

OBJECTIVE: A reappraisal of major papers was undertaken with the purpose to examine legitimacy of current restrictive transfusion strategy generalization dynamics.

METHODS: One to one critical revisit is selected for specific influential papers. Effort is made for a delineation of individual paper characteristics and subsequent data incorporation into a structural scheme proposal with sole purpose to land on a robust evidence estimation. The authors insist on issues of perception and stand on the reader's side instead of that of a writer or a member of a peer review team.

CONCLUSION: Settling at threshold of 7g/dl seems well supported but not definitely proven for ICU patients. Lower values for hemoglobin need not be discussed for the time being, since this level is already extremely austere. Results in this group should not be perceived as readily generalizable to common ward or outpatients, as they become achievable with simultaneous detailed monitoring and intensive functional support.

A. INTRODUCTION

There is nothing as good as pure blood when an indication for transfusion exists. In turn, blood is not regularly produced in a factory, so it must be thoughtfully collected out of alive volunteering persons. Blood resources utilization comes therefore to be a courteous administrative challenge. To transfuse means to infuse viable tissue elements in the circulatory system of the patient. Seen this way, administrating blood units simulates transplantation. Although standardization in procedures and products is strongly desirable, full automation in clinical decision making about need for transfusion is improper. On the other hand, full individualization of transfusion strategy could be perceived as proper and even desirable, yet it is not realistic. It may also be deceitful as a doctor's promise and vain as a patient's expectation. Clearly, we need

Conflict of Interest: None declared

modern techniques and policy standards for this frequently needed and conducted procedure.

Fundamentally, indications must be documented and reactions recorded as thoroughly as possible.[1] Hospital Transfusion Committees may undertake a supervisory role, but the real challenge is the co-operation of the Blood Bank with clinical departments. Departments need a common language to facilitate communication reciprocity. Thresholds as commonly accepted triggering values for transfusion appertain to this. Intensive Care Unit (ICU) remains attractive for safe clinical investigation including that for transfusion thresholds, as it makes use of multidisciplinary modalities for parameterization and timely intervention.

Anemia is very common in critically ill patients. Pathophysiology is multifactorial and multistage, whereas morphology is that of anemia of chronic disease.[2] It could be presented as an acute and threatening form of anemia of chronic disease. Hemoglobin value has been used for staging as it relates to DO2 and is an easily obtainable and communicable number.[3] Anemia, as expressed by hemoglobin values, has often been related in literature with worse overall prognosis. This is very confounded as a result because of incongruous retrospective data use in metanalyses and additional alteration by accompanying transfusions.[4]

To avoid irrelevant interpretations, some aspects of the critical anemia issue must be elucidated. First, severity of disease as depicted in Acute Physiology and Chronic Health Evaluation II (APACHE II), which is remarkably unique among ICU disease severity scores for incorporating anemia grading, is defectively estimating this special aspect of illness, as the vast majority of patients in the ICU according to this system would be uniformly given two points for an hematocrit of 20-29,9%.[5] Second, the depth of anemia is going deeper than values considered decisive in perioperative fields.[4] Third, orientation of ICU efforts points to maintenance of oxygen consumption for the sake of aerobic metabolism and this has also other ways to be pursued (e.g. ventilation and circulation assistance). Obviously, Hb and DO_2 are not so directly related in circumstances like this.[3] Last but not least, hematocrit restoration in near normal levels in the critical illness context is in reality unachievable, whatever the number of units utilized. In fact, satisfactory responses to transfusion rather point to the patient surpassing the critical stage of disease.[6]

Transfusion has been studied more efficiently than anemia in conjunction with mortality.[7] Results tend to be different between surgery and ICU studies.[8] Although surgical patients seem to enjoy overall benefit, ICU patients take only short-term advantage. Lack of uniformity of results allows for many meta-analyses which tend to favor the notion that regular transfusion accompanies worsening of hospital outcomes.[9]

Doubts about efficacy, partial futility, influence on outcome and even necessity of transfusion since other oxygen delivery improving manipulations are available have led intensivists to accept in principle the attitude of posing low cut-offs to hemoglobin values as a prerequisite for transfusion. The ICU has therefore become the leading research department for the substantiation of the transfusion threshold concept.

Besides quantity of transfusions, their quality has been set under investigation also. Leucoreduction has been found to be helpful[10] if applied on a wide basis and age of blood used seems not to be crucial when it lies in usual storage range.[11]

Transitivity in methods of clinical approving transfusions and blood bank practices during the last twenty years has made post hoc recapitulation of study data necessary for a reader to shape an opinion. This will be attempted below, focusing on the clinical use of thresholds.

B. MAIN THEME

1. CURRENT GUIDELINES

The basic scheme proposed by the British Society for Hematology (BSH),[12] based on all available information until 2013 is given in figure 1.

FIGURE 1. Guidelines by BHS-JPAC.

2. PLAIN VIEW OF PAPERS

a. Transfusion Requirements in Critical Care- TRICC trial

Design: The fundamental study involving critically ill patients is the TRICC (Transfusion Requirements in Critical Care, TRICC) trial by Paul Hebert et al for the Canadian Critical Care Trial Group in 1999.[13] Even now it is the only multicenter trial exploring this subject for general ICU population. The trial was conducted in 25 Canadian hospitals from 1994 to 1997. The presence of anemia with euvolemia and anticipated ICU stay of more than 3 days constituted the inclusion criteria. Intravascular volume was monitored and optimized by the intensive care unit specialized personnel. Exclusion criteria, besides null expectation for survival and preexistent anemia, consisted of the absence of active bleeding and cardiac surgery admission. Patients were divided into 2 groups: the restricted one with transfusion threshold of 7mg/dl and hemoglobin maintenance between 7-9g/dl and the liberal one with transfusion threshold of 10 mg/dl and hemoglobin maintenance between 10-12g/dl. Randomization included stratification for acute physiology and chronic health evaluation score (APACHE 2 score) and hospital, with further restriction to permuted blocks within strata. Central co-ordination consisted of generating random numbers in blocks of 4 to 6 in double for every hospital, enclosing the numbers in sealed envelopes, distributing the envelopes to centers and receiving periodically returned envelopes for inspection.

Outcomes and results: Death from any cause at 30 days was the primary outcome. Death at 60 days, death in hospital,

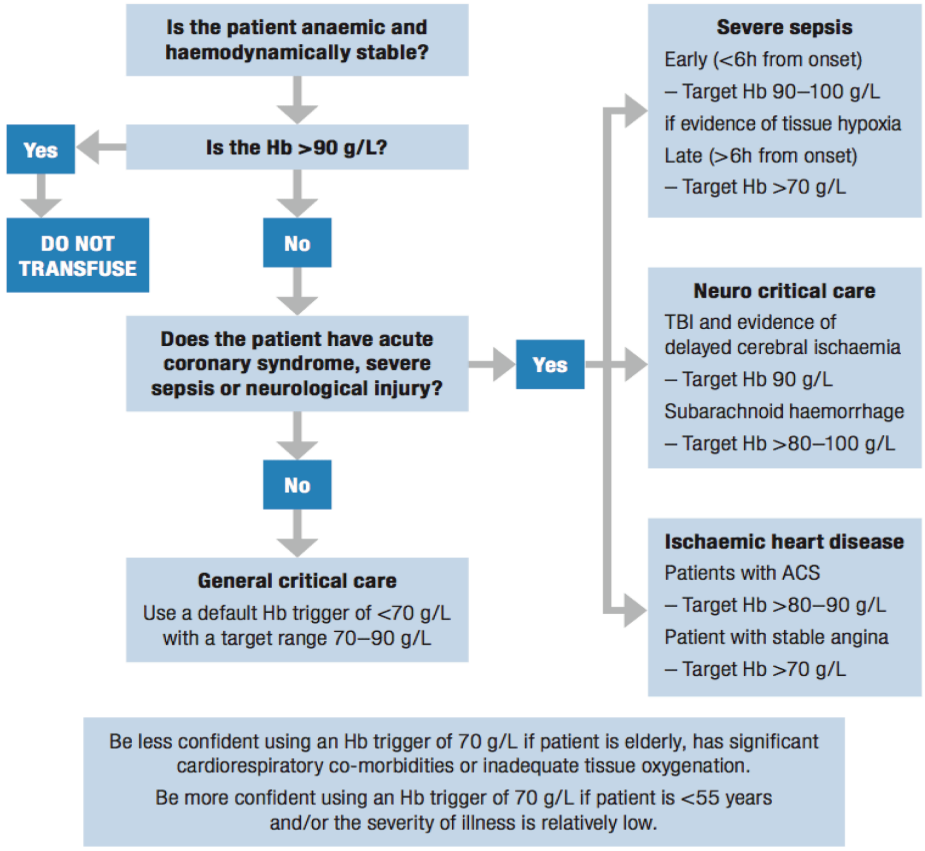

FIGURE 1. Directions from BHS and JPAC (10), 2013 [permission for use given].

death in ICU, duration of hospitalization, length of ICU stay and quantitative measures of organ dysfunction were all secondary outcomes. 838 patients were randomized. Analysis was conducted by the intention to treat principle (ITT). Baseline characteristics were similar in the two groups and pointed to patients of at least moderate severity as >80% were connected to a ventilator and the mean APACHE 2 score was 21. Primary outcome did not show any difference between groups. Adjusted organ dysfunction scores and their alteration during ICU stay were better for the restriction group. Subgroup analysis disclosed an advantage in 30-day survival of the restrictive policy for young (<55 years) and milder illness populations (APACHE score II <20). Subgroups of patients with sepsis, trauma[14] or cardiovascular problems[15] behaved much the same irrespectively of group.

Comments: Issues arise about the statistical power and the quality of inference. TRICC was designed as an equivalence trial, that is, to show that restriction of transfusions would lead to a mortality result not more or less than 4% (2% on each side), compared to the 30-day mortality of the standard liberally transfused group, which was thought optimistically to be 20%. Bioequivalence as a design is mainly used in laboratory drug studies. From the outset it could be commented that equivalence is an ambitious target as it is oriented towards the lack of not a simple arithmetic but a standardized difference between the control and intervention groups. As such, it essentially makes use of bidirectional one-sided tests that determine the upper and lower boundary of confidence intervals. This is more demanding than relying on solitary one-sided or two-sided tests.[16] For this reason, sample power needed is the most sizeable compared to relevant statistical choices (non inferiority or superiority trials). The sample size depends on the selected percentage (lower deviation means greater sample, most influential), the rate of success of the standard trial arm of study (the greater this rate the greater the sample, less powerful influence), the combination of the above two and conventions for statistical errors.

The basic notions are: a) **the null hypothesis is that the two treatments are different**.[17] This is the opposite of the usual case. b) type 1 error is to reject this hypothesis when the

hypothesis is true, i.e. to argue that restricting transfusions is the same with liberal policy although that they are different in reality. This type is represented by p which in clinically oriented studies should be preserved to the usual 0,05 (instead of using p=0,10, which happens quite often in bio-equivalence trials), c) Type 2 error is to accept the null hypothesis when the hypothesis is false, i.e. to say that restricting policy is different than the liberal, when in reality they are the same in terms of mortality. This probability, which usually is confined to 20% and is a major determinant variable in sample size calculation is not mentioned across the whole paper. Instead, an interplay between targeted margin and baseline mortality is recorded. After an intermediate adoption of sample size of 1620 patients and difference of the 5,5% class, it settles the type 2 error **below 50%**.

What could be a correct margin of equivalence in such a study? The reasonable approach is to select a number which is related to the treatment result of the standard arm itself. The problem is that equivalence studies do not generally have a placebo group which would naturally function as a reference, so literature data are used instead.[17] In this case, not only control completely without transfusion would not be allowed either way for ethical reasons, but also relevant literature is lacking. Since there are no data to substantiate the improvement brought upon by transfusions for patients, the percentage chosen to be ruled out as a difference was already arbitrary. Soon it became also elasticated.

Simultaneously the mortality of the standard arm became puzzling. More specifically, the initially hypothesized baseline mortality of 20%, was in an interim analysis of 404 patients proved to be arithmetically 23%. Could such a little deviation be a source of trouble? An automatic calculator would charge about 180 more patients every arm to show the 4% margin. Moreover, looking back, numbers from initial assessment (6451 patients) to final randomization (838 patients) seem to collapse. From 6451 assessed, only 3206 are found eligible. Reasons for non-eligibility include active bleeding, chronic anemia but there is also a remarkable number of 818 patients who were deemed to stay in the ICU less than 24 hours. This is not very common in general ICU's of many countries, as the context of work is not always anesthesiologic. From 3206 patients, the number shrinks to 2039 for various rather administrative or blood bank-imposed reasons. And after that, 1201 refusals are conceded, either from the physician's or the family side, balanced between each other, which is absolutely reasonable in view of the entrepreneurial nature of the whole process. On such a subsiding ground, slight numerical departures from expected control mortality can truly derail sample size issues, both as to quality and quantity. 20 to 23% increase could prove finally serious enough. Further on, the estimation remains optimistic since an APACHE II score of 20-22 degrees corresponds to a mean hospital mortality 30-40%. To predict a low baseline mortality initially moderates sample size demands. To find in the end a low mortality is more serious because it uncovers a better sample quality, able to endure treatments of doubtful benefit. Still, both help to ease the job of equalization, since both tend to obscure benefit from the traditional generous liberal approach to transfusions.

But there is more. The standard arm here is the liberal strategy arm and the 23% percentage found is greater than the 18% percentage of death in 30 days found in the restrictive arm. The interim analysis was not preprogrammed and was probably propelled by safety worries. **Difference between arms instead moved to the opposite direction than initially thought**. Seemingly, this contrast created an impression of de facto equivalence. Investigators could have thought that this inverted difference between arms was not anymore in need of full empowerment to refuse the null hypothesis. This is something although that can't be declared officially. The study is said to have been stopped prematurely merely because of recruitment flow deceleration. Published p values for outcomes rather portray a quasi successful superiority trial in favor of transfusion restriction than the technical incapacity to decline the null hypothesis of difference in the context of an equivalence trial. Definitely, the sample size utilized makes us unable to recognize real similarity, because we are prone to find similarity everywhere due to obvious and unscheduled expansion of b-error and loss of statistical power.

Looking forward now, whenever a great lag between assessment and final inclusion is ascertained, we use to talk about compromised generalization potential. This is not fair for this case even in the context of the aforementioned statistical shortfall. Whatever patient is left behind, looks very much like the everyday life of the average ICU. The randomized population of patients is absolutely representative as it is numerous, of moderate severity, general in nature with all subgroups proportionally participating. The eligible person's profile was so clearly delineated, that grey zones were totally obstructed. Reasons of eligible population for non-entry to the study were free of bias as to the final result. Primary outcome recorded was unmixed and the only worth. We come to agree with the authors that findings can be readily generalized, as there is a respectable number of 838 patients and an impeccable distribution.

First hypothesis formation is acceptable in the field of mathematics in the face of full uncertainty. TRICC is a valuable piece of naove clinical investigation as its primal question is both daring and simple. It is also technically exemplary for its high level of achieved corroboration. Clinical constraint impeded statistical integration, but this is not to blame but to admire because it accompanies the trustworthiness of excellent clinical conduction. But at the end of the day, it remains clinically safer to state that restrictive and liberal policies are different when they really are the same than to accept identity when the two arms are in fact different. We could well cope with a slight allowance towards the first direction but not with the second.

Statistics are not TRICC's leverage, since clinical concerns have been more influential for its course. The trial is inadequately empowered to carry equivalence along. It is nevertheless the main study that contributes an important amount of data in meta-analyses, because one of its excellent characteristics is that it volunteers for future coalescence with other studies. According to older and more conservative perceptions about grades of evidence and recommendations, even if this trial would have come to a statistical end, the need for another confirming trial would still hold. More recently, level 1 evidence is achieved with only one randomized control trial with statistical completeness or systemic review of individual homogeneously targeted randomized trials.[18] The discussion below deals exactly with TRICC's awaited sequel.

b. Add-ons to TRICC: neurologic, pediatric and sepsis populations

Subgroups behaved much the same in TRICC trial. This was initially thought to mirror the relatively stable situation of the patients, e.g. what the authors mentioned as euvolemic patients. In essence, these were patients in the post-acute severity decelerating period, corresponding somewhere between the second or third phase of Pamplin's Phases of Illness Paradigm, (POIP) of hospital course.[19] Trauma patients need aggressive transfusion therapy when actively bleeding,[20] but thresholds hold for the postoperative and ICU stage. Traumatic brain injury is a separate class which is examined many times together with ischemic brain damage.[21] Data about brain damage have not changed. The major study about traumatic brain injury is that by Robertson et al[22] (EPO Severe TBI study) with 200 patients and a factorial design for simultaneous study of erythropoietin usefulness. The study did not show any advantage for liberal transfusion thresholds in this special kind of trauma. Nevertheless, worries about sensitivity of nervous cell to the vicious cycle of hypoxemic insult and edema, have preserved a transfusion threshold of 8 mg/dl for critical neurologic disease.[23] A new trial (HEMOglobin Transfusion Threshold in Traumatic Brain Injury Optimization: The EMOTION trial, ClinicalTrials.gov Identifier: NCT03260478,[24] with 762 patients in Canada) has been now undertaken in order to provide awaited answers.

The TRIPICU[25] trial by Lacroix et al, came to deal with the issue in Pediatrics. 627 children from 3 to 14 years old from 19 hospitals in 4 well developed countries entered the flow of a non-inferiority design with 10% margin. The two approaches (thresholds of 7 vs 9g/dl as transfusion triggers) did not differ at all as to a composite outcome of death and occurrence or worsening of MODS. The overall incidence of the outcome was only 12% though and reference estimation is not mentioned. Divergent profiles of outcome frequency and icu admission and length of stay profile between children and adults makes metanalytic mixing of results inappropriate. Separate convincing data are definitely needed for every group, especially for kids.

Regarding sepsis, the study by Rivers et al[26] (Early Goal Directed Therapy-EGDT-Collaborative Group study) interposed a threshold of 10mg/dl for the evolving septic shock, along with other interventions with fluids and inotropes. Rivers' study did not mention assumed baseline mortality but the anticipated mortality benefit was 15%. The results stood between 46,5% (standard arm) and 30,5% (experimental arm). Sample size was from one center and it was only 260 patients. It is tiny, especially bearing in mind the huge impact of forthcoming application. The whole tactic was challenged, although after 13 years, by newer trials in sepsis with more than 1000 patients each.[27-29] In the passage of time though, general application of protocols sticking to first-order manipulations in antibiotics and fluids is unfolded, leading to an upgrade of the whole emergency care context. In this evolutionary process, let us believe that the study by River and colleagues, beyond problems with single-center conduction and the absence of a reference mortality was fairly constructive. Naturally, the transfusion arm could nothing but change together with all other paths of the algorithm all the way through.

c. Transfusion Requirements in Septic Shock - TRISS study

The arrival at the section of transfusions in this setting is the study by Holst et al.[30]

Design: The study (Transfusion Requirements in Septic Shock, the TRISS trial), comes from 32 Scandinavian Hospitals between 2011 and 2013 and aims to confirm the restrictive policy concept for transfusion as well as to challenge the first 6 hours issue, posed by River's study. Randomization scheme included stratification for center and presence or absence of hematologic malignancy and permuted blocks of 6,8,10 patients at 1:1 proportion. Blinding in all these studies cannot be perfect as doctors need to know the intervention. Inclusion criteria were age greater than 18 years, ICU admission, septic shock and Hb less than 9g/dl. Exclusion criteria included active hemorrhage and active coronary artery disease. The thresholds chosen were 7mg/dl for the restriction policy arm and 9mg/dl for the 'standard' arm. In contrast with TRICC, all red blood cell units were leucodepleted.

Outcomes and results: Primary outcome chosen was 90-day mortality. Inotrope and mechanical ventilation use at day 5-14-28, complications, ischemic events, days free of support until the 90th day, days alive and out of hospital until the 90th day constituted secondary outcomes.

Comments: This was a superiority trial, which is less demanding than equivalence in terms of sample size. Baseline mortality was taken as 45% and desired improvement was taken as 9%. Given these numbers, in Holst's study, a power of 80% and p value of 0,05, sample size was calculated at the number of 1000 patients. Analysis was conducted according to ITT principle and was complemented by per protocol (PP) analysis as violations were more on the restrictive side

(45 vs 16 patients). An interim analysis was programmed for 500 patients. Study flow from assessment for eligibility to randomization and follow up was exceptionally tight with 1224 assessed, 1005 randomized and 998 included in final analysis. Severity was rather mild to moderate and about 50% of patients belonged to medical wards and had respiratory infections. Mortality was as expected (43 vs 45%). No difference was found in any outcome or subgroup (age><75yrs, APACHE 2><53, cardiovascular disease). In principle, failing to reveal superiority does not mean equivalence in statistical terms. Moreover, violations of protocol were significant and necessitated an additional PP approach. This need is itself an issue because the usual analysis selection is the ITT, the PP results given only when in concordance. In other case, more statistical work-up is warranted and possible problems about publication arise. These violations concerned both allowing units to the restricted group and restricting units for the liberally treated patients. The whole effect could well be a degree of mitigation. On the contrary, uniform use of leucodepleted products is an advantage since it isolates one of the confusing factors, enhancing possible transfusion benefits.

Transfusion during the first 6 hours, a matter posed by Rivers et al and supposed to be one of the questions that TRISS would explore, is not answered in reality, as all patients are seated in the ICU at randomization, and time data from the Emergency Department (ED) are not mentioned. Rather this issue has been overcome not by TRISS itself but by the synchronous constellation of studies targeted to the early care of sepsis.[26,27] We do not know how many patients in TRISS had received rescue transfusion. In case this number was great, it could mitigate results even more, as what has been done in the first place seems to be decisive for whatever will follow. Transfusing to catch a decent hemoglobin value instead, is confirmed to be explicitly futile, as the majority of patients received over three red blood cell units in the liberal group, whereas most patients in the restrictive side consumed one or zero units. These findings, quoted in the supplementary appendix[29] of the study, expose both mortality-hemoglobin dissociation and hemoglobin-transfusion intensity lack of proportional response.

The compactness of this study is nearly beyond belief. Sepsis is a condition whose outcome is dependent more on the Health and Hospital system than on the patient himself. Even though percentage of mortality falls within the widely reported range, control of patients in all stages must have been very effective. This is a crucial obstacle to generalization since other countries suffer from prehospital and hospital system inadequacies. The time from TRICC to TRISS and beyond certainly has played a role, in terms not only of modification of standard care, but also intermediate consolidation of restrictive practice (in other words, **de facto reconciliation to equivalence**) and improvement of blood bank product quality. TRISS trial, although narrowly targeted, is the most relevant to TRICC in terms of their potential to merge with one another.

d. Exclusions of TRICC

Building up confidence to the scientific significance of a study can be done in two ways. The first is to multiplicate it and directly confirm it, which is the traditional straight selection, exemplified as precisely as possible in the case of TRICC with TRISS and TRIPICU studies. An alternative is to surround it with data from excluded populations in the first study, which resembles a circumferential or marginal approach. Crudely, if the argument still holds in the feared case, it holds even more in the rule area. In words of reasoning, clarifying boundaries helps to elucidate concepts within. The two major excluded categories in TRICC were active bleeding and cardiac surgery. Recent studies venture into these territories.

i. Acute Hemorrhage:

Active bleeding is a recognized indication for transfusion, something that is clearly mentioned in guidelines.[12,31] Surgical control of blood loss is fundamental in many cases. Transfusions are used in this life saving setting rather liberally in order to protect the operational conduction and result but are rationalized thereafter. To raise an argument in favor of transfusion restriction already at the outset means in principle to stay behind direct surgical interests.

The Villanueva (ESTudio RAndomizado y controlado de los requerimientos Transfusionales en la hemorragia digestiva alta aguda, ESTRAT) study

Design: The study by Villanueva et al,[32] is engaged in upper gastrointestinal bleeding, a situation used to be conservatively managed in the first place. The study was conducted in only one center in Barcelona between 2006 and 2009 and included 921 patients. Acute coronary disease, lower gastrointestinal bleeding and patients with a great probability of re-bleeding or death as estimated by the Rockall score were excluded along with other typical exclusions. Transfusion thresholds and hemoglobin ranges chosen were 7-9g/dl and 9-11g/dl. As in all studies about transfusions, blinding could not be complete. Randomization scheme consisted of stratification according to presence of hepatic cirrhosis and use of blocks of 4. All patients received a first unit of red blood cells. The units were leucodepleted and had a mean hematocrit of 60% which is rather low. Treatment consisted of immediate endoscopy and local treatment with electrocautery, ligation or cyanoacrylate infusion and drug therapy with omeprazole or somatostatin. Some patients with cirrhosis underwent also hepatic venous pressure gradient measurement.

Outcomes and results: Primary outcome chosen was 45-day mortality, whereas re-bleeding and complications were set as secondary outcomes. Design referred to a superiority trial, assuming 10% baseline mortality and 5% reduction by restrictive handling of transfusions. Analysis run according

to ITT principle and subgroups pre-specified concerned only presence or absence of cirrhosis. From 1610 patients assessed for eligibility 962 were confirmed as such and finally 921 were randomized. 49% had peptic ulcer and 31% had cirrhosis. Besides reduction in units given in the restrictive group, an advantage of restriction policy over standard manipulation appeared (23 vs 41 patients). Re-bleeding, length of stay, rescue surgeries, hepatic venous pressure gradient and complications were all better in the restrictive group.

Comments: This study is single centered and reflects mainly the clinical efficiency of the responsible team in this hospital. The baseline mortality was small as predicted and this facilitates fulfillment of sample size demands. Severely ill patients were excluded, which enables mortality to remain low. Even though the population of restriction group as a whole behaved better, the advantage is more profound on cirrhosis patients and implies involvement of specific mechanisms as hepatic venous pressure also indicates, like some form of circulation impediment in visceral vein vasculature. The message is rather that transfusion for bleedings of upper gastrointestinal origin can be minimized, if indicated diagnostic and treatment interventions are provided in a timely and safe fashion. Under certain circumstances like cirrhosis, volume or viscosity related challenge with transfusion may even be harmful. This is a motive-creating finding for the team in charge. Overall, it is the only study with pure mortality as a primary outcome that sets foot on superiority, but it pertains to patients outside the icu and thus its additivity to TRICC is questionable, as is also its repeatability on a multicenter basis. The Transfusion in Gastrointestinal bleeding (TRIGGER) trial[33] is the sequel. It is a feasibility study with cluster design, undertaken as a precursor of a multicenter properly empowered study to reply to the repeatability and generalization to the hospital reality of the ESTRAT study. Whereas cluster design with counting on hospitals instead of patients as units of power, seemed to facilitate recruitment, homogeneity in emergency action during the first 6 hours across hospital proved problematic to achieve. Outcomes did not differ but results are only indicative.

Primal findings of endeavors like the above two studies, suggest that hemorrhage is not fully incompatible with some kind of transfusion economy, provided that hemostatic manipulations are well targeted, timely and adequate.

ii. Cardiac Surgery:

This is a field that yields dual concerns since it is applied at first to cardiovascular patients which subsequently, after the discrete surgical hit, fall into the critically ill category. Two large randomized studies dominate here at present:

1) Transfusion Indication Threshold Reduction - The TITRE-2 study

TITRE-2 study by Murphy et al[34] came first to fill the gap. Baseline knowledge about use of red blood cell units in cardiac surgery is readily commented in the background. Whereas more than 50% of patients are transfused, the range of transfusion frequency is extremely wide in pioneer countries such as UK and USA, which highlights that it is the availability of blood that matters more than performance of transfusions itself.

Design: This was a prospective multicenter study in 17 hospitals in UK between 2009 and 2013 and included adult patients scheduled for elective surgery of several types. Septic and emergency patients were excluded. Randomization scheme consisted of detecting patients with postoperative hemoglobin value of 9 g/dl or less, and allocation according to cohort minimization which implies stratification according to centers and leads always to well balanced samples. Patients remained blinded. Selected thresholds were 7,5 and 9 g/dl, which were tougher than the previously used. Liberally treated patients received a single red blood cell unit as a bonus immediately after randomization.

Outcomes and results: The primary outcome was composite, consisting of 90-day appearance of ischemic events and infections. Mortality here was a backstage secondary target along with length of stay, individual elements of the composite outcome, quality of life, adherence to protocol and cost. This study used conclusions of a previous study from the same contributors in 2007. Baseline acceptances were drawn from this former study and were 11% and 17% incidence of the outcome in the restrictive and liberal group respectively. From the sample size calculation, one can understand that this was conceived as a superiority study with 90% power, trying to declare the formerly shown difference as statistically important. There was no prediction for interim analysis. From 8428 eligible patients, 3565 gave written consent and 2007 were randomized from which the vast majority was included in analysis. Intention to treat principle was used in analysis. 63% patients of the restrictive group received at least one unit of red blood cells and 26% of patients received at least one unit before randomization. Severe non adherence was slightly more common in the restrictive group and not statistically checked. Results were surprising in that although the primary outcome affected the same percentage of patients (33 vs 35%), there were statistically more deaths in the restrictive arm (4,2 vs 2,6% or 42 vs 26 deaths, p=0,045).

Comments: The choice of outcome served the practical purpose of a more manageable size compared to mortality. Sensitivity analysis by adding acute kidney injury or subtracting patients transfused prior to randomization, further enhanced the distance between arms in favor of the liberal strategy. Remarkably, the centre with the greater contribution (382 patients out of a total of 2003 patients, with usual numbers falling between 100-150 patients/centre) whose name is not mentioned, was the only one that gave clear results favoring liberal manipulation. Data assert that stinginess in transfusions is at least not superior to a liberal approach. One interesting comment about chosen thresholds is that by choosing 9g/dl

for the liberal arm, the investigators pushed 1288 patients out of study since they moved in higher hemoglobin values. Supposedly the liberal threshold was defined in the order of 10g/dl -as in other studies like Hajjar's- this numerous population would have entered the study. The anticipated influence for such a mix experiment with good quality patients could have restrained mortality from becoming apparent. Now, trying to prove superiority and ending up with more mortality is defective and doubtfully repeatable as an attempt.

2) Transfusion Requirements in Cardiac Surgery Trial – TRICS III study

This study by Mazer et al[35] was published in the end of 2017, as an adequately powered answer to the Titre-2 study.

Design: this was an open-label multicentric study. It was supported by Canada and Australia Health Institutes for Blood Services and recruited participants from 79 hospitals settled in 19 countries from 2014 to 2017. It compared restrictive transfusional strategy with threshold Hb 7,5g/dl to the liberal option with transfusional threshold of Hb 9,5g/dl or 8,5g/dl (ICU or common ward respectively). Randomization took place before the operation and the resulting strategy was applied in the perioperative period too. Euroscore as a prognostic inclusion criterion was set at 6 or more, which means a moderate to high surgical risk. A composite of death and other complications was defined as the outcome of interest. Baseline incidence was considered to be about 11% and sample power was calculated in a non-inferiority context with $\delta=3\%$, aiming at an one-sided a-error of 0,025 and a b-error of 85 initially and later 90%. Pilot TRICS II study patients were incorporated all along. Primal analysis was conducted by the PP methodology. Although randomization blocks were attributed to every site, no stratification according to centre in the context of primal analyses was used.

Results and outcomes: 5243 patients were randomized, 5092 consisted the modified ITT population and 4860 were included in the PP analysis, which is a tight flow course. Primary outcome did not differ between groups, so non-inferiority was reached. Patients over 75 years were found to take a small advantage of transfusion restrictions whereas length of stay in ICU and hospital as well as delirium incidence were found to favor slightly the liberal group.

Comments: Statistical success is the first to admit after reading this study, as the sample was adequate to face mortality issues and initial acceptances were strict and realistic. Patients were plenty and sufficiently ill. The threshold of 9.5 g/dl for the liberal group has gathered many good quality patients inside, so maybe a soothering population mix, which was not present in Titre-2 has ensued. There is one comment that should be made. Hemoglobin move in values of 8.5 to 9.5 g/dl in both groups and all the stages of care which is importantly higher than the threshold of 7.5 g/dl which could according to working hypothesis jeopardize outcomes. Whereas this was also a feature in Titre-2, here the distance between the lower Hb tested in working hypothesis and that observed in the study is greater (approximately 8,5 and 8g/dl respectively). In comparison to Titre-2 study, here we have early randomization, much more patients, much more centers, greater euroscore, less overall transfusions though, probably less operational complexity, probably better functional status of patients, perioperative secondary outcomes description such as low output syndrome, shorter follow-up for primary outcome (28 vs 90 days) and no perioperative blood saving procedures description. Overcoming the arithmetical issue, the presence of too many hospitals and discordance between euroscore prognostic evaluation and clinical data (predicted and observed mortality >6% and 3% respectively) raise an issue of selection bias. In the introduction of Titre-2, a comment is made about variations in transfusion rates. It is possible that TRICS-III took advantage of routine ambiguity about need for transfusion so that participation in a famous running study worked as an extra motive for responsible personnel. Not refusing the attractiveness of a numerous sample, we support the case that Titre-2 was much more tight as it was conducted in a single country, achieve proportionally faster rates of patient recruitment and also was more consistent with simple medical principles, like cautiousness about perioperative issues. To conclude, despite the presence of two multicentric studies, evidence for the special area of cardiac surgery has not been integrated yet.

e. The cardiologic case- Myocardial Ischemia and Transfusion (MINT) pilot study

Cardiac surgery patients' manipulation cannot fall into core restrictive perceptions. They function rather as a signal for the wide cardiovascular category of patients for whom final conclusions have not been yet drawn. It's again time to take a long jump entirely out of the ICU territory to identify exceptional patient characteristics and bring them back within. Carson et al have published a pilot study strictly focusing on the cardiac subject.[36]

Design: This was a pilot study with 110 patients from 8 US hospitals with stable or unstable coronary disease in the way to cardiac catheterization. Chosen thresholds for transfusion were 8 or symptoms restrictively and 10g/dl liberally. From the registration number we understand that this is the entryway to the MINT study (Myocardial Ischemia and Transfusion). Randomization included stratification according to center and stable or unstable disease and the use of blocks. The selected primary outcome was a composite of death, myocardial infarction or need for emergent revascularization in 30 days. Also, a number of other outcomes relating to mortality, ischemic events and complications were recorded.

Outcomes and results: Details about calculation of sample size are not given, but the pilot trial stopped early in 110 patients and not 200 as initially planned, after the decision of the supervising committee. From 1920 assessed patients, only

110 were included, the reasons being mainly milder anemia, refusals, critical illness and need for emergency surgery. All patient entered analysis which was done by intention to treat. Leucoreduction was not a precondition, although it had been conducted finally in the vast majority. The age of red blood cells is one of the greatest in related studies. The flow of study revealed that **the outcome happened more often in the restrictive arm** (14 vs 6 pts, 25% vs 10%, p=0.054). Especially death with 1 in liberal and 7 events in the restrictive arm, proved to be also statistically significant. The trial was disrupted before the difference could become able to substantiate difference and the reason given was that it was decided to leave some space for other studies.

Comments: Timing of randomization in relation to catheterization is not mentioned. Moreover, global conduction of catheterization on the same admission is not confirmed in the text. Age is greater in the restrictive arm. Patients in this arm had less often stable angina, had less often undergone PCI, had more 3-vessels disease and more anemia before transfusions. In other words, it was a group with more severe health distortion and worse prognosis. Liberal patients maintained the value of 10g/dl arithmetically, whereas restricted patients had to express symptoms of fall to 8g/dl if it were to receive blood. In view of more severe disease and need for conservative treatment, the contrast between the generosity for the first and stinginess for the second group is provocative. Is this a protocol defect or a kind of clinical bias in order to protect interventional success? Surely anyway, is an adequate reason to pause the conduction of the study.

Half the matter is about a single unit of blood as can be seen in the table of transfusional data. Thus allowing for one unit a priori, maintaining hemoglobin values above 8 g/dl regardless of symptoms, and having equalized disease severity and maximized revascularization in both groups would be fairer. Anemic patients are deeply ill in the coronary disease setting and probably more dependent on adequate hemoglobin. In view though of its weaknesses, MINT is an aggregate of well balanced between hospitals groups of patients, initialized and interrupted by reasonable concerns. This brings us back to clinical naivety of the TRICC trial. Effort for the formal conduction of MINT trial is ongoing, without important protocol modifications with the exception of encouraging transfusion in Hb <7g/dl, There are accompanying public concerns about ethics and adequacy of information in the consent form.[37,38] Maybe investigators consider cardiac disease as a challenge, but pilot data, even in the face of group dissimilarities are disappointing. As for general ICU patients, they are prone to have underestimated coronary artery disease and should not be left to elude in the otherwise noisy general critical context.

f. Meta-analytic progress in the mean time

Systematic reviews[39,40] in general suffer from inadequate homogeneity in this field. Cochrane and Holst's metanalyses, although without retrospective element included, function more as aggregates of various studies in terms of kind and quality. More sophisticated statistical methods (e.g. trial sequence technique in Holst et al paper in BJM) do not guarantee level of evidence establishment, as they deal with statistical but not clinical inhomogeneity. Salpeter's effort[41] is focused exclusively on achieving homogeneity but this does not seem to be accomplished as studies like TRICC and Villanueva study are obviously dissimilar in terms of patient populations included. All reviews point to restrictive strategy as most proper but this comes up more as a result of preformed author volition and less as an unbiased arithmetic result which is the main issue in gathering studies together. The specific category of cardiovascular disease has been addressed in the metanalysis by Docherty and Walsh, where a more lenient threshold is proposed, albeit unitizing again disparate proportions of patients coming from miscellaneous studies, all before 2013.[42]

The most obvious aspect of bias is timing of publication as this always coincides with the arrival of restriction encouraging studies. TRICC remains the cornerstone of all these metanalytical efforts. It would be certainly preferable to reproduce the results of TRICC with another study with general patient population. Currently, TRISS resembles TRICC more than every other study but again it is focused only on sepsis patients. Maybe also the combination of Titre-2 with TRICS III can offer a degree of support. Based on a combination of TRICC with systemic reviews of studies with modest homogeneity, the achieved level of evidence is considered to be presented as 1b. **To upgrade to 1a, or even to stabilize 1b means at least another study like TRICC.** Threshold of 7g/dl may be in the mean time applied and evaluated inside the ICU but is not subject to extrapolations to other patient populations approaching, like perioperative patients.[43]

3. CONCLUSION

First priority must be to preserve an adequate minimum level of hemoglobin concentration instead of full restoration. Presence of anemia influences outcome but transfusion should be regarded too complicated as a solution. As full Individualization of the indication for transfusion is rather immodest as a uniform hospital proposal,[4,44] we need a general direction represented by the triggering threshold suggestion. Applicability of restriction thresholds depends on respect on appropriateness, critical illness staging and estimation of comorbidities.[45-47] The rule of 7 g/dl seems to be well supported for the time being, although not irrevocably proven. **Sensitive subpopulations pointed out by scientific associations[12] still hold, with the exception of early septic patients which can cope with low threshold and growing worries about cardiovascular patients.** Clinical investigation concerns are more reliable to steer transformations of routine practice than statistical

formatting. Both are needed though to substantiate indisputable evidence. Improvements in a wide array of therapeutic protocols have surpassed liberal hemoglobin goals and should be incorporated in hospital practice throughout the world.

Intensive care units offer multidisciplinary monitoring and therapy. This should not be over-interpreted, as we think that is happening with the 'new normal' concept.[48] Non critical patients most often can't tolerate a hemoglobin value fall to 7 g/dl either acute or chronic. Thresholds like this are excessively austere in the face of jeopardized reserves and must be tightly anchored with sufficient scientific data and supporting frame. Our clinical approach as to symptoms and signs interpretation is anticipated to change. Interestingly, ultimate consequences of critical illness like cognitive dysfunction, persistent paralysis due to neuromyopathy or non-healing pressure ulcers have not been studied in connection to transfusion tactics met in the first place.[49] At present, a descent compromise has been reached between blood resources use rationalization, evidence base medicine principles compliance and critical illness causality. Like pharmacologic investigations in the post marketing stage, conservative thresholds need now to be stabilized, consistently applied and globally evaluated for a significant period of time.[50]

ACKNOWLEDGEMENT

We would like to acknowledge Dr Chris Koutsarnakis, Neurosurgeon. He presented of a version of the evidence-confidence scheme in his 2017 Evaggelismos Hospital Annual Seminar lecture about latest Neurosurgery Clinic education initiatives. Thanks for sharing in turn his interesting (both as to form and content) idea with us.

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