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2008 Emily Cooley Memorial Lecture Lessons Learned from Pediatric Transfusion Medicine Clinical Trials ... A Little Child Shall Lead Them

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Abstract

Background—Many clinical practices in transfusion medicine are controversial and/or lack definitive guidelines established by sound clinical trials. Although recommendations based on results of clinical trials performed using infants and children may not always be applied directly to adults — and vice versa — lessons learned from pediatric trials can be useful when critically assessing the design/results/conclusions of adult trials.

Methods—Four randomized clinical trials (RCTs) studying pediatric patients were critically reviewed. They addressed two RBC transfusion issues: (1) transfusion guidelines by which RBC transfusions are “triggered” by liberal (high pretransfusion patient hematocrit levels) versus being “triggered” by restricted (low pretransfusion hematocrit levels); and (2) transfusion of fresh RBCs (≤ 7 days storage) versus RBCs (up to 42 days storage).

Results—Findings established by primary outcomes generally were firm (eg, fewer RBC transfusions were given to infants/children managed by restricted guidelines; transfusing small volumes of RBCs stored up to 42 days to preterm infants diminished allogeneic donor exposures and were equally efficacious and safe as fresh RBCs stored ≤ 7 days). Findings based on secondary outcomes, subset and *post hoc* analyses were inconsistent (eg, clinical outcomes were equivalent following liberal or restricted transfusions in only two of three RCTs; in the third, more neurological problems were found in neonates given restricted transfusions).

Conclusions—Clinical practices should be based on data pertaining to the primary outcomes of RCTs, as trials are designed and statistically powered to address these issues. Clinical practices suggested by analysis of secondary outcomes, subsets of patients and *post hoc* analyses, should be applied cautiously until studied further — ideally, as primary outcomes in subsequent RCTs.

Introduction

Many transfusion medicine practices are controversial and vary greatly among physicians because of insufficient definitive information. In clinical settings, decisions are based on logical assumptions, experience, judgment and an honest effort to do what is best for the patient. However, assumptions that seem almost irrefutably logical can be proven to be incorrect when actually studied, and decisions based on the best of intentions sometimes are found later to be harmful — hence, the need to practice “evidence-based medicine.” The cornerstone of evidence-based medicine is to test relevant hypotheses by well-designed (ie, experimentally and statistically sound), randomized clinical trials (RCTs) that will establish

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efficacy, detect toxicity and utilize healthcare resources optimally by recommending care for those most likely to benefit (ie, proven efficacy with acceptable toxicity) and withholding care (and avoiding risk/toxicity) when benefit is unlikely.(1)

Several RCTs of transfusion therapy have been conducted in pediatric patients (ie, neonates, infants and children), and it is worthwhile to critically assess these reports because pediatric patients often provide a fairly homogeneous/uncomplicated population in whom to test hypotheses (ie, generally, they do not have as many confounding conditions due to aging and previous medical disorders as do adults). We have often heard pediatricians say “Children are not small adults,” when they caution that data from RCTs in adults cannot be directly applied to children because physiology and pathophysiology may vary with age. By the same token “Adults are not large children,” and the results of pediatric RCTs must be applied to older patients cautiously. With these caveats in mind, it is useful to examine how lessons learned from pediatric RCTs might be applied to RCTs involving adults.

Although many controversial practices exist in transfusion medicine, this paper will focus on two current issues pertaining to red blood cell (RBC) transfusions: (1) use of liberal versus restricted “transfusion triggers” to determine the optimal pretransfusion hematocrit (HCT) at which to transfuse critically-ill patients; and (2) selection of fresh versus stored RBC units for transfusion. Four RCTs studying pediatric patients will be critically analyzed in terms of their design, conduct, results, conclusions, limitations and possible application of the lessons learned to the analysis of RCTs involving adult patients.

Liberal (LIB) versus Restricted (RES) RBC Transfusion Programs

Despite millions of RBC transfusions given annually for many decades and literally countless publications dealing with RBC physiology, the pathophysiology of anemia and disorders of RBC dysfunction and the effects of RBC transfusions, little definitive information exists to permit precise recommendations for the optimal pretransfusion hemoglobin concentration to prompt (ie, trigger) a RBC transfusion or for the optimal post-transfusion HCT needed to achieve the goal of correcting and maintaining normal tissue oxygenation in patients with anemia and/or RBC dysfunction. Excessive RBC transfusions (ie, “overtransfusion”) will increase both the known and still undefined risks of blood transfusions, whereas, insufficient RBC transfusions (ie, “undertransfusion”) may increase problems resulting from inadequate tissue oxygenation. Accordingly, RCTs have been conducted, both in pediatric and adult patients, to compare the efficacy and possible toxicity of LIB vs RES RBC transfusion guidelines/programs. Although specific details vary among these RCTs, the general design is to compare RBC transfusions given at relatively high pretransfusion patient HCT levels (ie, LIB transfusion “trigger”) versus transfusions given at relatively low pretransfusion HCT levels (ie, RES transfusion “trigger”).

The goals and hypotheses to be tested by RCTs comparing LIB vs RES RBC transfusions are designed to answer one or more of the following questions. Are fewer RBC transfusions given or are fewer patients transfused when RES programs are followed? Is the efficacy of RBC transfusions given per RES and LIB programs equivalent or is one program superior? Are adverse effects or undesired clinical outcomes equivalent or are they increased in patients given RBC transfusions per LIB or RES programs? Generally, one of these goals is selected as the primary outcome, and the RCT is designed and powered statistically to test the stated hypothesis. The other goals, usually, are secondary outcomes with the significance of differences between groups determined by analysis of subsets of patients, composite endpoints or *post hoc* analysis for which the RCT, often, has neither been designed nor statistically powered *a priori* to give definitive answers. Although differences between patient groups or study arms for some of these secondary outcomes do reach statistical

significance, conclusions may be misleading or even found to be incorrect when tested, subsequently, as primary endpoints in properly-designed RCTs.

RCTs with neonates and infants—Two RCTs compared RBC transfusions given per LIB vs RES programs to preterm neonates/infants with the anemia of prematurity,(2,3) and two commentaries about these RCTs have been published.(4,5) The RCT from Iowa(2) was a randomized, unblinded trial with the primary outcome to determine if RBC transfusions would be reduced in infants given RBC transfusions by a RES program. Clinical status of neonates assigned to RES vs LIB groups was compared/assessed by multiple secondary outcomes measured throughout the duration of the RCT. Preterm neonates with birth weight (bw) between 0.5 kg and 1.3 kg were enrolled; infants with heart disease, hemolysis or likely imminent death were excluded. All transfusions were given as 15 mL/kg of prestorage leukocyte-reduced RBCs stored up to 42 days. The pretransfusion HCT that would “trigger” a RBC transfusion was determined by the pulmonary clinical status of each neonate/infant at the time the transfusion was prescribed. When intubated and receiving oxygen via mechanical ventilation, pretransfusion HCT levels were 46% (LIB) vs 34% (RES). When receiving oxygen without mechanical ventilation, pretransfusion HCTs were 38% (LIB) vs 28% (RES). When oxygen was no longer needed, pretransfusion HCTs were 30% (LIB) vs 22% (RES). Thus, differences in pretransfusion HCT levels between LIB and RES groups ranged from a high of 12 to a low of 8 HCT percentage points.

The RCT from Canada(3) was a multicenter, randomized, unblinded trial to determine if RBC transfusions given per LIB or RES programs affected a composite primary outcome of either death or of survival with severe retinopathy of prematurity, bronchopulmonary dysplasia or severe brain injury detected by ultrasound examination. Other clinical outcomes and use of RBC transfusions were compared by secondary outcomes. Preterm neonates with bw <1.0 kg were enrolled; infants with possible extra RBC needs (eg, surgery or hemolysis) or imminent death were excluded. All transfusions were given as 15 mL/kg of washed “packed” RBCs. Beyond washing, there was no mention of further leukocyte-reduction by filtration or of the duration of storage. Pretransfusion HCT levels to “trigger” RBC transfusions were determined by two linked factors at the time the transfusion was prescribed — age (≤ 7 days of life, 8-14 days and ≥ 15 days) and whether or not the neonate was receiving respiratory support. When respiratory support was needed, the pretransfusion HCT varied with age and ranged from 41% to 30% (LIB) vs 35% to 26% (RES). When respiratory support was not needed, the pretransfusion HCT ranged from 36% to 26% (LIB) vs 30% to 23% (RES). Thus, differences in pretransfusion HCT levels between LIB and RES groups ranged from a high of 6 to a low of 3 HCT percentage points. [NOTE: Patient pretransfusion Hb/dL values, as reported in the paper,(3) were multiplied by three to convert Hb to HCT values for the comparisons done here.]

To understand comparative results and conclusions of these two RCTs, several points must be emphasized about the pretransfusion HCT “trigger” values and the resulting patient blood HCT levels maintained with or without RBC transfusions. The differences in pretransfusion HCT values (ie, levels that determined the threshold for giving a RBC transfusion) between LIB and RES groups in Iowa were much greater than in Canada (ie, 8 to 12 HCT percentage points in Iowa vs 3 to 6 HCT percentage points in Canada). The average difference in blood HCT values maintained in LIB vs RES infants in Iowa was much greater than in Canada (ie, 9 HCT percentage points in Iowa = Hb of 2.7 g/dL vs 3 HCT percentage points in Canada = Hb of 1.1 g/dL). Thus, infants in the LIB and RES groups in Iowa were quite different hematologically from each other because of these large HCT differences, likely, creating biological/physiological differences between study groups. In contrast, because of the relatively small differences in HCT levels between infants in the two study groups in Canada, the question can be raised as to whether infants in the LIB and RES groups in

Canada really were sufficiently different hematologically and physiologically to exhibit clinically significant differences in outcomes.(5)

Both studies found fewer RBC transfusions given per the RES program, but the finding of fewer transfusions was expressed in different ways. In Iowa,(2) 12% of LIB infants vs 10% of RES infants avoided all RBC transfusions (no significant difference). However, among transfused infants, those in the LIB group received 5.2 ± 5 RBC transfusions per infant vs 3.3 ± 3 in the RES group ($p = 0.025$). In Canada,(3) 5% of LIB infants vs 11% of RES infants avoided all RBC transfusions ($p = 0.037$), but the number of RBC transfusions per infant was not significantly different (5.7 ± 5 LIB vs 4.9 ± 4 RES). Many clinical outcomes, which were evaluated individually as secondary outcomes, were not significantly different between LIB and RES groups in both RCTs(2,3) — including death, bronchopulmonary dysplasia, patent ductus arteriosus, retinopathy of prematurity, growth and need for oxygen (Table 1).

Although most clinical outcomes in both RCTs were similar whether infants received RBC transfusions per LIB or RES programs, infants in Iowa, who were transfused per RES lower pretransfusion HCT levels, exhibited significantly more ($p = 0.004$) severe apnea plus grade 4 intraventricular hemorrhage and/or periventricular leukomalacia* (*post hoc* composite outcome) than those in the LIB group (Table 2). Canadian infants exhibited no differences between LIB vs RES groups in terms of apnea or severe brain injury (Table 2). When trying to understand the discordant findings of the two RCTs, it is important to remember two facts. First, the Iowa findings were based on a *post hoc* analysis of a composite outcome, for which the RCT was neither designed nor powered *a priori* to assess definitively.(2,4,5) Second, over 70% of Canadian infants exhibited very serious clinical conditions (composite primary outcome), whether in the LIB or RES RBC transfusion program (Table 2) — making it extremely difficult to detect a significantly worse outcome in either group (ie, additional adverse effects caused by either under or over transfusion).

The discordant/contrary findings of the two RCTs place physicians prescribing RBC transfusions for preterm infants in a quandary. On one hand, results of the Iowa RCT plus additional, although indirect, information from two sources suggest that the higher blood HCT levels, maintained in the Iowa RES group, may have protected the brain of preterm infants. Kissack et al(6) reported an association between brain hemorrhage and/or infarction and high cerebral fractional oxygen extraction in a comparative study of 25 preterm infants — who were similar overall, except 13 had brain injury and 12 did not. The authors concluded that low cerebral oxygen delivery was a mechanism involved in brain injury and that high cerebral fractional oxygen extraction was an indicator of poor brain oxygenation. Since low blood HCT is a cause of low cerebral oxygen delivery and likely poor brain oxygenation, the findings support the concept that HCT levels following RBC transfusions might influence hemorrhagic brain injury in preterm infants. Consistent with this rationale, Mercer et al(7) reported that transfusion of autologous placental blood, accomplished by delayed umbilical cord clamping, increased neonatal HCT levels and decreased intraventricular hemorrhage in preterm infants (14% of infants with hemorrhage following delayed vs 36% following immediate cord clamping).

On the other hand, because microvascular blood flow and tissue perfusion/oxygenation can be adversely affected by high blood HCT levels — particularly, as a consequence of transfusing stored RBCs(8-10) — the possibility must not be overlooked that

*Injury to the white matter of the brain due to softening and damage to the brain tissue near the cerebral ventricles. Premature infants are at greatest risk of this entity which can lead to motor control problems, developmental delays, and cerebral palsy or epilepsy later in life.

overtransfusion due to LIB programs might, also, pose dangers (ie, presumed benefits of higher blood HCTs are negated by diminished microvascular blood flow and poor cerebral oxygenation). Until additional RCTs are performed, with brain injury studied as the primary outcome, and information becomes available about the long-term development of transfused infants — studies are now being performed with the Iowa infants, who are now approximately 12 years of age — it seems prudent to transfuse RBCs to neonates/infants per standard guidelines¹¹ and to avoid either extremely high or low pretransfusion HCT levels (ie, to transfuse per LIB or RES programs only in approved investigational settings with parental informed consent).

RCT with older infants and children—One RCT, comparing LIB and RES RBC transfusion guidelines in infants and children admitted to pediatric intensive care units (PICU), will be discussed here as an example of a study performed in a setting other than the neonatal intensive care unit (NICU). Lacroix et al⁽¹²⁾ reported a multicenter, partially blinded RTC (ie, those monitoring safety of the trial and analyzing data were blinded, but patients/parents and those involved in the clinical care of the patients were not blinded to the assigned transfusion program) with a noninferiority statistical design. The hypothesis tested was that LIB and RES RBC transfusion programs would be equivalent [ie, there would be <10% difference in the development of new or progressive multiorgan dysfunction (MOD) — the primary outcome of the RCT].

The 637 patients included in the final intention-to-treat analysis were highly selected (ie, 88% of PICU patients initially evaluated were excluded at the outset for several reasons including acute blood loss, cardiovascular problems, weight <3.0 kg or a NICU infant, hemolytic anemia, hemodynamically unstable, etc. Of the remaining unexcluded patients who were eligible to give consent, only 63% were randomized.⁽¹²⁾ Patients in the LIB group were transfused with RBCs (prestorage leukocyte-reduced, but anticoagulant/preservative solution and storage age not reported) when the patient Hb level was <9.5 g/dL, with the goal to increase the blood Hb by 1.5 to 2.5 g/dL. Patients in the RES group were transfused similarly when the patient Hb was <7.0 g/dL. Notably, a substantial difference ($p<0.001$) in mean patient Hb levels was maintained between the two patient groups with or without RBC transfusions (LIB = 10.8 g/dL vs RES = 8.7 g/dL for a difference of 2.1 g/dL).

By intention-to-treat analysis, rates of new or progressive MOD (primary outcome) were 12% in both groups.⁽¹²⁾ Thus, RBC transfusions given per LIB or RES guidelines were equivalent per the MOD outcome, despite 44% fewer RBC transfusions given to RES patients. In fact, 54% of RES patients were given no RBC transfusions at all vs only 2% of untransfused LIB patients.⁽¹²⁾ Although intention-to-treat analysis (ie, to include every patient randomly assigned in the analysis whether or not they experience the intervention — RBC transfusions in this RCT) is the “Holy Grail” of RCTs, when the aim of a RCT is to assess the effects of transfusions (ie, efficacy and possible toxicity), it seems reasonable to, also, include a subset/secondary analysis of the comparative results of patients *actually* transfused and experiencing the possible benefits and adverse effects of transfusions. In this RCT, results of an analysis of transfused patients would have been particularly interesting because *transfused patients* given RBCs per RES guidelines received *more* transfusions (although, not statistically more) than *transfused patients* in the LIB arm (LIB = 1.7 RBC transfusions per transfused patient vs RES = 2.1 RBCs per transfused patient)^{!(12)}

Several factors must be remembered when applying the results of this RCT⁽¹²⁾ to transfusion practice. First, this RCT was not designed to demonstrate superiority of either LIB or RES RBC transfusion guidelines, so claims of superiority must be taken cautiously. Second, the patients actually studied were highly selected, so results can not be applied broadly to all children admitted to a PICU. Third, the children studied received somewhat

modest transfusion support (ie, 90% of patients were given $\leq$ two RBC transfusions with a total volume of RBCs transfused $\cong$ 20 mL/kg/patient, and <10% of patients received plasma and/or platelet transfusions), so results can not be applied to patients requiring more extensive transfusion therapy.

Fresh versus Stored RBC Transfusions

The goal of RBC transfusions is to normalize tissue oxygenation in patients with clinically significant anemia and/or RBC dysfunction. However, the efficacy of RBC transfusions in achieving this goal has been difficult to establish and, in some instances, RBC transfusions actually have been suggested to increase morbidity and mortality — particularly, when the transfused RBC units have been stored for longer than two to three weeks.(13-19) Although the superiority of transfusing only fresh RBCs (ie, units stored no longer than 7 to 10 days) has not been definitively proven by large, well-designed RCTs, the “storage lesions” known to occur in RBC units during blood bank storage make compelling arguments that transfusions of older/stored RBCs might pose dangers — especially when given in large volumes to critically-ill patients.

These “storage lesions” include decreased levels of RBC adenosine triphosphate and 2,3-diphosphoglycerate (2,3-DPG), altered RBC shape with decreased deformability, decreased hemoglobin-bound nitric oxide, and accumulation in the extracellular storage fluid of cytokines, microparticles/vesicles and microaggregates consisting of cells, cell fragments and fibrin. These “lesions” became progressively more extensive as the duration of storage lengthens, are only partially abrogated by prestorage leukocyte-reduction, can not be eliminated by filtration at the time of transfusion, and logically, can be presumed to diminish microvascular blood flow — the last of which likely contributes to tissue ischemia. Although many reports exist either to support or to question the merits of transfusing only “fresh” RBC units and/or only leukocyte-reduced blood products,(13,19-24) scientifically-sound RCTs have not provided widely accepted guidelines for clinical transfusion practice.

For decades, physicians treating preterm infants have debated the need to transfuse only “fresh” RBC units (usually defined as stored $\leq$ 7 days) versus accepting “stored” RBC units (usually defined as up to the permitted storage limit for the anticoagulant/preservative solution used by the local blood bank — ie, usually 35 or 42 days since donation). Physicians supporting transfusions of only “fresh” RBCs have four concerns about transfusing “stored” RBCs to preterm infants: (1) the accumulation of potentially toxic substances in the extracellular storage fluid such as potassium, ammonia, RBC-free hemoglobin and acidic ions; (2) the possible risks of constituents/additives present in RBC anticoagulant/preservation solutions; (3) poor oxygen off-loading due to loss of RBC 2,3-DPG; and (4) diminished microvascular blood-flow due to misshapen and poorly deformable RBCs. Physicians supporting transfusions of “stored” RBCs, as a means to diminish the risks of allogeneic donor exposures, believe that these four concerns do not pose significant risks to preterm infants for small-volume (ie, 15 mL/kg infant weight at the time of transfusion) RBC transfusions.(11,25-26)

Although several RCTs have compared the effects of transfusions of RBCs from fresh vs stored units to preterm infants, only one of them will be discussed here.(27) Neonates with bw 0.6 to 1.3 kg were randomly assigned to receive all small volume (15 mL/kg) RBC transfusions from units stored $\leq$ 7 days in citrate-phosphate-dextrose-adenine (CPDA) or from units stored $\leq$ 42 days in AS-1 solution. Although blood bank staff knew the group assignment to dispense RBCs for transfusion, parents, NICU physicians and staff and investigators conducting the RCT were blinded to the type of RBCs transfused. The primary outcome was to document a significant decrease in allogeneic donor exposures in neonates given stored AS-1 RBCs, with many secondary outcomes assessing both efficacy (eg, post-

transfusion increase in neonatal HCT and *in vivo* RBC recovery and survival) and possible toxicity (eg, post-transfusion changes in neonatal plasma electrolytes and chemistries, levels of RBC 2,3-DPG, transfusion reactions and clinical status).(27)

In the CPDA group, 21 neonates received 58 RBC transfusions — 100% stored ≤ 7 days — with a mean donor exposure rate of 3.7 donors per neonate. In the AS-1 group, 19 neonates received 66 RBC transfusions — 47% of which were stored ≥ 15 days — with a mean donor exposure rate of 1.6 donors per neonate. Thus, the primary endpoint of fewer donor exposures with stored AS-1 RBCs was met ($p < 0.05$).(27) Both efficacy and safety of AS-1 stored RBCs were demonstrated by the results of pretransfusion versus post-transfusion laboratory studies (Table 3), by the absence of transfusion reactions, and by the lack of differences between fresh CPDA and stored AS-1 groups in serum creatinine, bilirubin, alanine aminotransferase and aspartic aminotransferase levels and in RBC 2,3-DPG levels. (27)

The authors concluded that AS-1 RBCs, transfused as multiple 15 mL/kg aliquots taken from a dedicated unit stored up to 42 days, could safely provide all small volume transfusion needs of preterm infants — thus, reducing allogeneic donor exposures.(27) As reviewed,(26) these conclusions have been supported by several RCTs, including one of almost identical design to the AS-1 vs CPDA study(27) assessing RBCs stored in AS-3.(28) In an important study of a subset of these infants, the comparative post-transfusion *in vivo* 24-hour recovery and survival of biotinylated AS-3 RBCs was nearly identical with RBCs from fresh or stored units.(29)

Lessons Learned from Pediatric Transfusion RCTs

Pediatric and adult patients differ physiologically; the pathophysiology of diseases/disorders requiring RBC transfusions, likewise, may differ in pediatric and adult patients; and the response to RBC transfusions may vary according to age. Accordingly, results and recommendations for practice based on results of RCTs performed using pediatric or adult patients cannot be interchanged “automatically” from one group to another — particularly, when neonates/infants are involved. However, some of the lessons learned from the critical analysis of the pediatric RCTs assessed here can be applied broadly.

First, to detect clinically significant differences and to draw meaningful conclusions when comparing the effects of RBC transfusions given per LIB vs RES transfusion guidelines, the study groups must truly differ significantly hematologically/physiologically/biologically. There must be substantial differences both in the pretransfusion patient HCT values “triggering” RBC transfusions and in the overall patient HCT levels maintained with or without transfusions (ie, these HCT values/levels must be substantially higher in LIB vs RES patient groups so that the difference between groups is clinically significant). These differences were achieved in two of the pediatric RCTs,(2,13) but was not achieved in the third.(3) In a widely-cited RCT comparing LIB vs RES RBC transfusion guidelines in adult patients,(30) both of these goals were achieved — a difference of 2.0 g/dL pretransfusion Hb concentration (ie, HCT $\cong$ 6%) between LIB and RES RBC pretransfusion “triggers” and a difference of 2.2 g/dL (ie, HCT $\cong$ 6 to 7%) in daily patient blood Hb levels.

Second, results/conclusions most likely to be correct and not to be refuted by other RCTs are those established by assessment of the primary outcome/endpoint — because RCTs are designed and powered statistically for this purpose. Results/conclusions arising from secondary outcomes/endpoints, analysis of subsets of patients or *post hoc* analysis — particularly of *post hoc* composite outcomes — may be misleading and may not be confirmed when more rigorously assessed as primary endpoints in subsequent RCTs. For example, the discordant findings pertaining to possible brain injury in preterm infants

receiving RBC transfusions per RES guidelines in Iowa were raised by *post hoc* analysis of composite outcomes and need additional study before being accepted as truly valid.(3,6) Although the RCT from Canada(4) did not agree with this finding, the Canadian data — for several reasons discussed earlier — do not provide definitive information to resolve the dilemma. Therefore, pediatricians/neonatologists must await results of subsequent RCTs before clearly knowing optimal transfusion practices.

Third, the temptation to overextend the results/conclusions must be resisted — regardless of how correct/logical/trendy such extensions seem to be. When RCTs are reported in high-quality journals with rigorous peer-review, the experimental/statistical design will be described in detail — as will any changes made during conduct of the RCT and/or during analysis/reporting of the data, along with cautionary statements by the authors. In addition, cautionary statements sometimes will be made by experts in accompanying commentaries. Unfortunately, these details/caveats are not always appreciated by readers, and findings that the authors may state as needing further investigation or being preliminary are accepted as truths that lead, prematurely, to changes in clinical practice that have not achieved “evidence-based” status.

For example, it was clearly stated by Lacroix et al(12) that RBC transfusions given to stable, critically-ill children per RES guidelines decreased RBC transfusion requirements without increasing adverse outcomes — as supported by assessing the primary outcome of new or progressive MOD. Also, stated in the report(12) were the facts: that neither LIB nor RES guidelines could be proven inferior or superior because the RCT was designed as equivalence trial; that the study subjects were highly-selected due to fairly extensive exclusion criteria; that RES RBC transfusion guidelines were suspended (ie, discontinued to permit RBC transfusions at more liberal pretransfusion HCT levels) in 14% of subjects for a mean of 3.3 days; that transfusion support was somewhat modest; and that two scoring systems used to estimate the extent of patient illness indicated only a modest degree of illness in the study subjects.(12) Thus, the temptation to transfuse RBCs per RES guidelines to all or most children admitted to the PICU — rather than applying the results only to patients similar to those actually studied in the RCT — would be a clear overextension of the results/conclusions of the RCT and must be resisted.

Similarly, the conclusion permitted by assessment of the primary endpoint of the oft-cited RCT of Hébert et al(30) was that the 30 day mortality was similar in adult patients given RBC transfusion per LIB vs RES transfusion guidelines. Because it was an equivalency trial, neither transfusion program could be proven superior or inferior, when all patients were assessed per intention-to-treat analysis. The report(3) clearly stated: that only 13% of assessed patients were consented/randomized (ie, study subjects were highly-selected); that RBC units transfused were stored without leukocyte-reduction in CPDA solution (storage age when RBCs were transfused was not specified); that mid-study changes were made in experimental/statistical design for the number of patients to be enrolled, and end-study changes were made for analysis of a subset of patients based on APACHE II scores (severity of illness scores); that analyses were performed by intention-to-treat, despite one-third of RES patients never being transfused and, accordingly, experiencing neither possible benefit nor toxicity due to transfusions; that, despite analysis of many secondary outcomes, of many subsets/subgroups of patients, and of composite outcomes “to improve our ability to detect meaningful differences” between patient groups, no statistical adjustments were made for multiple comparisons (ie, differences were considered to be statistically significant when the overall two-sided alpha level was ≤ 0.05). Although all of these caveats/cautionary statements were made by the authors, they concluded that “our conclusions may be generalized to most critically ill patients — with the possible exception of patients with active coronary ischemic syndromes.”(30) Although others agree with this sweeping

conclusion, based on my preceding comments/discussion, I believe that such broad application is an unsupported overextension of the data/results of their RCT.

Final Conclusions

When critically analyzing RCTs and considering their possible application to clinical practice, assess the following: (1) scientific rigor of the experimental and statistical design; (2) the clinical relevance/importance of the questions/hypothesis being investigated; (3) the characteristics of the patients being both studied and excluded; (4) limitations of the design/results/conclusions of the RCT as stated by the authors and, perhaps by other experts, in accompanying editorials/commentaries; (5) support, or lack thereof, by other published RCTs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Strauss RG. Meta-analysis and evidence-based decision-making in neonatal care. *Dev Hematol Immunol*. 2005; 39:253–262.
2. Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, Cress CA, Johnson KJ, Kromer IJ, Zimmerman MB. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics*. 2005; 115:1685–1669. [PubMed: 15930233]
3. Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, Peliowski A, Rios A, LaCorte M, Connelly R, Barrington K, Roberts RS. The premature infants in need of transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr*. 2006; 149:301–307. [PubMed: 16939737]
4. Bell EF. Transfusion thresholds for preterm infants: how low should we go? *J Pediatr*. 2006; 149:287–289. [PubMed: 16939732]
5. Strauss RG. Commentary: Is it safe to limit allogeneic red blood cell transfusions to neonates? *Neonatology*. 2008; 93:217–222. [PubMed: 18025793]
6. Kissack CM, Garr R, Wardle SP, Weindling AM. Postnatal changes in cerebral oxygen extraction in the preterm infant are associated with intraventricular hemorrhage and hemorrhagic parenchymal infarction but not periventricular leukomalacia. *Pediatr Res*. 2004; 56:111–116. [PubMed: 15152052]
7. Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage late-onset sepsis: a randomized, controlled trial. *Pediatrics*. 2006; 117:1235–1242. [PubMed: 16585320]
8. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA*. 1993; 269:3024–3029. [PubMed: 8501845]
9. Tsai AG, Cabrales P, Intaglietta M. Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. *Transfusion*. 2004; 44:1626–1634. [PubMed: 15504169]
10. Simak J, Gelderman MP. Cell membrane microparticles in blood and blood products: potentially pathogenic agents and diagnostic markers. *Trans Med Rev*. 2006; 20:1–26.
11. Strauss RG. How I transfuse red blood cells and platelets to infants. *Transfusion*. 2008; 48:209–217. [PubMed: 18194380]
12. Lacroix J, Hébert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, Gauvin F, Collet JP, Toledano BJ, Robillard P, Joffe A, Biarent D, Meert K, Peters MJ. TRIPICU Investigators;

- Canadian Critical Care Trials Group; Pediatric Acute Lung Injury and Sepsis Investigators Network. Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med*. 2007; 356:1609–1619. [PubMed: 17442904]
13. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med*. 2008; 358:1229–1239. [PubMed: 18354101]
 14. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, Moliterno DJ, Lindblad L, Pieper K, Topol EJ, Stamler JS, Califf RM. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA*. 2004; 292:1555–1562. [PubMed: 15467057]
 15. Zallen G, Offner PJ, Moore EE, Blackwell J, Ciesla DJ, Gabriel J, Denny C, Silliman CC. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *Am J Surg*. 1999; 178:570–572. [PubMed: 10670874]
 16. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma*. 2003; 54:898–905. discussion – 905-907. [PubMed: 12777902]
 17. Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Arch Surg*. 1997; 132:620–624. discussion 624-625. [PubMed: 9197854]
 18. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation*. 2007; 116:2544–2552. [PubMed: 17998460]
 19. Vamvakas EC, Carven JH. Length of storage of transfused red cells and postoperative morbidity in patients undergoing coronary artery bypass graft surgery. *Transfusion*. 2000; 40:101–109. [PubMed: 10644819]
 20. Tsai AG, Cabrales P, Intaglietta M. Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. *Transfusion*. 2004; 44:1626–1634. [PubMed: 15504169]
 21. Walsh TS, McArdle F, McLellan SA, Maciver C, Maginnis M, Prescott RJ, McClelland DB. Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? *Crit Care Med*. 2004; 32:364–371. [PubMed: 14758149]
 22. Hébert PC, Chin-Yee I, Fergusson D, Blajchman M, Martineau R, Clinch J, Olberg B. A pilot trial evaluating the clinical effects of prolonged storage of red cells. *Anesth Analg*. 2005; 100:1433–1438. [PubMed: 15845701]
 23. van de Watering L, Lorinser J, Versteegh M, Westendorp R, Brand A. Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. *Transfusion*. 2006; 46:1712–1718. [PubMed: 17002627]
 24. Bilgin YM, van de Watering LM, Eijssman L, Versteegh MI, Brand R, van Oers MH, Brand A. Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. *Circulation*. 2004; 109:2755–2760. [PubMed: 15148271]
 25. Strauss RG. Blood component transfusion for infants. In: Simon, TL.; Snyder, EL.; Solheim, BG.; Stowell, CP.; Strauss, RG.; Petrides, M., editors. *Rossi's Principles of Transfusion Medicine*. 4th. Bethesda, MD: AABB Press; 2008. in press
 26. Strauss RG. Data-driven blood banking practices for neonatal RBC transfusions. *Transfusion*. 2000; 40:1528–1540. [PubMed: 11134575]
 27. Strauss RG, Burmeister LF, Johnson K, James T, Miller J, Cordle DG, Bell EF, Ludwig GA. AS-1 red cells for neonatal transfusions — a randomized trial assessing donor exposure and safety. *Transfusion*. 1996; 36:873–878. [PubMed: 8863773]
 28. Strauss RG, Burmeister LF, Johnson K, Cress G, Cordle D. Feasibility and safety of AS-3 red blood cells for neonatal transfusions. *J Pediatr*. 2000; 136:215–219. [PubMed: 10657828]
 29. Strauss RG, Mock DM, Widness JA, Johnson K, Cress G, Schmidt RL. Post-transfusion 24-hour recovery and subsequent survival of allogeneic red blood cells in the bloodstream of newborn infants. *Transfusion*. 2004; 44:871–876. [PubMed: 15157254]

30. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999; 340:409–417. [PubMed: 9971864]

Table 1

Clinical outcomes with no statistically significant differences* in infants given RBC transfusions per liberal (LIB) vs restricted (RES) programs in Iowa(2) or Canada.(3)

Outcome	IOWA		CANADA	
	LIB	RES	LIB	RES
Death	2% *	4%	18%	22%
Bronchopulmonary dysplasia	38%	35%	56%	59%
Patent ductus arteriosus	43%	39%	—	—
Retinopathy of prematurity	4%	4%	18%	19%
Growth	No differences		No differences	
Oxygen needs	No differences		No differences	

* Percentage of infants exhibiting this endpoint. Statistical comparisons are between Iowa Lib vs RES and Canada LIB vs RES; not Iowa vs Canada.

Table 2

Severe outcomes following RBC transfusions given to infants in Iowa(2) or Canada(3) per liberal (LIB) or restricted (RES) programs.

Outcomes	IOWA *	
	LIB	RES
Severe apnea (episodes/day)	0.43	0.84
Grade 4 intraventricular hemorrhage (% infants)	0%	8%
Periventricular leukomalacia (% infants)	0%	14%
	CANADA **	
Severe apnea	60%	55%
Ultrasound brain injury	21%	19%
Death or survival with severe ROP, BPD, brain injury	70%	74%

* Iowa: More apnea and brain injury in RES infants (p=0.004).

** Canada: No differences in apnea or severe outcomes (p>0.2).

ROP = Retinopathy of prematurity; BPD = Bronchopulmonary dysplasia.

Table 3

Changes in laboratory tests results (post-transfusion values minus pretransfusion values) following 15 mL/kg transfusions of RBCs from either CPDA units stored ≤ 7 days or AS-1 units stored ≤ 42 days. No statistically or clinically significant differences were found comparing CPDA vs AS-1 transfusions.

Analyte	CPDA	AS-1
HCT %	+12	+12
Glucose (mg/dL)	-9	-9
Lactate (mmol/L)	-0.3	-0.1
pH	0.0	0.0
Ca (mg/dL)	-0.1	-0.1
Na (mEq/L)	+0.5	+0.6
K (mEq/L)	+0.3	-0.2