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Routine use of newer (fresher) RBC products

A Blood Bank Technologist who works at a hospital in Northeastern Wisconsin reports that the recently published article in the New England Journal of Medicine has had a **major impact** at his institution. Since the publication, their **heart surgeons now insist that all RBC products must be less than 2 week old**, to avoid transfusing RBCs that have suffered a detrimental 'storage lesion'. He is concerned that this new ordering behavior **could create a local blood shortage situation**, especially if more and more physicians request RBCs that are less than 2 week old blood for all their patients. The inquiring colleague would like to know **what other institutions are doing** with regards to routinely providing RBC products that are less than 2 weeks old, when requested. As an additional point, upon reviewing the NEJM article, the inquiring colleague did **not see any subgroup comparisons** between patients who only received **leukocyte reduced newe**r blood products versus only received **leukocyte reduced older** blood products, since there are data to suggest that the storage lesion of RBCs is somewhat mitigated by pre-storage leukocyte reduction.

The following comments have been submitted.

ADDENDA Mar. 28, 2008

1. **Dr. Harvey G. Klein, Chief, Department of Transfusion Medicine Clinical Center at the National Institutes of Health** (attribution used with permission) comments that the retrospective analysis of red cell age and complications of open heart surgery is the latest of several analyses of the age of blood transfused and patient outcome. He points out that this **report is notable** because it is the **largest such analysis from a single institution** and because it is sufficiently large to permit analysis of groups that received only blood stored more than 2 weeks versus blood less than 2 weeks old. However, as has been repeated on numerous occasions, such analyses are **helpful for formulating hypotheses to be tested prospectively**, but **should not form the basis for changes in medical policy**. As large and as carefully-analyzed as this study is, it is clear that there are **major differences** in the **clinical features of the two groups**. For example, a greater percentage of patients receiving older blood had abnormal left ventricular function, mitral regurgitation, and peripheral vascular disease. There were undoubtedly other patient differences that we assume are balanced when large prospective randomized trials are conducted - but exist in retrospectively defined cohorts. **Multivariate analysis cannot change this**. Differing numbers of patients were tested for several variables - a common and usually unavoidable weakness of retrospective studies. There is probably no increased risk in preferring blood that is stored for less than 2 weeks (although Dr. Klein points out that the **risk of cell-associated viruses and graft-versus-host disease appears to be increased in fresher blood**), but neither does **this study provide sufficient scientific basis to modify current transfusion practice**.

ADDENDA Mar. 30, 2008

2. **Dr. Aryeh Shander, Chief of the Department of Anesthesiology, Critical Care Medicine, Pain Management and Hyperbaric Medicine at Englewood Hospital in New Jersey** (attribution used with permission), comments that he **agrees with the comments made by Dr. Harvey Klein**. Dr. Shander also comments that the patients who got 'older' blood at the Cleveland Clinic got more units than did the patients who got younger blood. Data from many similar studies suggest that there is a **dose relationship between the amount of blood received and poorer outcomes (more is worse)**. This could also skew the results of the Cleveland Clinic study especially when blood does not need to wait 14 days to be 'old'. In Dr. Shander's opinion the **pressure on the blood supply will continue to rise** as these and other data get published while the Food and Drug Administration and the Centers for Medicare and Medicaid Services keep **restricting the use of erythopoietin stimulating agents**.

ADDENDA Mar. 31, 2008

3. **Dr. Neil Blumberg, Director of Clinical Laboratories at the Strong Memorial Hospital at the University of Rochester Medical Center in Rochester, NY** (attribution used with permission) comments that the increased mortality of cardiac surgery patients who received 'older' blood at the Cleveland Clinic may have been due to **'uncontrolled' confounders**, since the **data were collected as part of an observational study**. One 'red flag' that uncontrolled confounders are at play is that the recipients of the older blood received more leukocyte-reduced transfusions than did the recipients of younger blood, yet the older blood recipients had poorer outcomes. Dr. Blumberg points out that randomized trial data from numerous studies demonstrate that mortality rates of cardiac surgery patients who receive exclusively leukocyte-reduced blood products is reduced by 30-50%. Since the **data in the Cleveland Clinic's study are uncontrolled and non-randomized,** any **interpretation drawn from these data must be viewed with caution**. Dr. Blumberg wonders why the authors at Cleveland Clinic continue to transfuse non-leukocyte-reduced blood products to cardiac surgery patients, given the literature on the subject. A second red flag to consider is that **group O patients are greatly over-represented among the patients who received younger blood**. According to Dr. Blumberg's experience (as yet unpublished data), Group O patients may be at lower risk of thrombosis and multi-organ failure syndromes. Furthermore, the excess deaths in the patients who got older blood are not in the category of cardiac deaths, e.g., MI, stroke, arrhythmias, but infection, organ failure, etc. This is not what he would expect from the effects of storage on red cells based upon animal model data. Thus on balance, Dr. Blumberg thinks the authors may have come to a **correct conclusion**, that storage damage increases risk to patients, but that the data presented in the NEJM article **do not remotely prove that the use of older blood was the key reason** for the poorer outcomes of the patients who received it.

   Dr. Blumberg provides his views as to how to reduce the risks of transfusions to cardiac surgery patients. Firstly, all transfusions should be leukocyte-reduced because leukocyte-reduction appears to reduce the incidence of pulmonary failure in critically ill patients (e.g., ARDS, TRALI) Thus **leukocyte-reduction** is far and away the **most important thing one can do for transfusions to cardiac surgery patients**. In order to make sure that all transfusions are leukocyte-reduced, **universal leukocyte-reduction of the hospital's blood supply is necessary to ensure not running out** of leukocyte-reduced red cells for these patients. Secondly, he believes that **avoiding ABO mismatched platelet, FFP and cryoprecipitate** transfusions is a relatively simple practice that is much more important to good clinical outcomes and has better data in its support than worrying about storage period. Thus, giving **younger blood without leukocyte-reducing transfusions is likely to be a waste of time and resources**. He adds that even fresh blood that is rich in leukocytes and platelets is going to be more dangerous than older leukocyte-reduced blood to cardiac surgery patients. He reminds us that in Van de Watering's original randomized trial published in Circulation in 1998, post-storage leukocyte-reduction was as effective as pre-storage leukocyte-reduction in reducing mortality in cardiac surgery. This proves, to Dr. Blumberg's way of thinking, that leukocyte-reduction is more important than shortening the blood product's storage period.

   In summary, Dr. Blumberg says that **his hospital has no plans to give cardiac surgery patients only fresher (younger) blood**, because he believes that his hospital is doing interventions (leukocyte-reduction and ABO matching) with more data in support, and that the NEJM data are not convincing.

ADDENDA April 4, 2008

4. **Dr. Ronald A. Sacher, Professor, Internal Medicine and Pathology at the University of Cincinnati Academic Health Center and Director, Hoxworth Blood Center** (attribution used with permission) reports that he has no doubt that stored blood undergoes changes and that some of these "storage lesions ' may be less advantageous than fresh blood to certain patient populations. He points out that current additive solutions enable blood to be stored for 42 days and there are **well documented changes that compromise oxygen delivery** (2,3 DPG reductions), **endovascular function** (depletion of nitric oxide), and **red cell survival**, as well as **enhance inflammatory mediators** (e.g., IL-6 amongst many others). The recent retrospective study published in the NEJM from the Cleveland Clinic raises a question about the benefit of using younger blood in cardiac surgery patients. Their data showed that older blood (>14 days) is associated with more post-operative complications. **Two previous small randomized controlled trials (RCT) in adults** [Schulman CI, et al. J Trauma. 2002;52:1224-5 and Walsh et al. Crit Care Med 2004; 32:364 –371] **did not demonstrate any harm from prolonged storage of RBC units**. The **problem with the current NEJM report** is that this trial was retrospective and therefore the **patient populations being compared were not equivalent**. For example, as pointed out by Dr. Blumberg, there was a disproportionate use of Group O blood between the two study groups, which can confound the data. Dr. Sacher agrees

with Dr. Klein's comments that multivariate analysis cannot change the obvious flaws of retrospective studies. Furthermore as Dr. Shander points out, **the patients who received older blood got more of it than the patients who got younger blood** and there are data supporting the fact that more blood is well known to be associated with an adverse outcome.

It is therefore Dr. Sacher's **opinion that whilst this study raises questions, it certainly does not answer them** and **his academic canter will not change practice** and **will not** at this stage identify special fresh inventories for this patient population.

Dr. Sacher adds: "In this day and age when **blood transfusion demand is up** (5% at our center over the last year), when the perceived donor base is substantially less than previously believed and with the baby boomers are now requiring blood rather than donating it, not to mention the concerns about erythrocyte stimulating agents, there is **considerable pressure to maintain optimal inventories**. Demands for decreased storage times will severely compromise blood availability with its own adverse outcomes. Research undertaken at Hoxworth Blood Center has shown that a more physiological solution pioneered by Dr.Tibor Greenwalt has distinct advantages over the standard solutions that have been around for many years. Perhaps this is the time to **re-explore alternative storage solutions with demonstrated benefits**".

ADDENDA April 15, 2008

5. **Dr. Martin H. Ellis of the Meir Medical Center, Kfar Saba** and his colleague, **Dr. Noga Manny of the Hadassah University Medical Center in Jerusalem** (attribution used with permission) would like to suggest an **alternative method of analysis of the data** published the NEJM paper by Koch et al entitled "Duration of red-cell storage and complications after cardiac surgery" published recently, and **receive feedback regarding this suggestion**. They feel that the **14-day cut-off point** used by the authors to **define new versus old blood** converts storage duration from a continuous to a discrete variable and is **artificial**. They would be interested to know the outcome of correlative analysis performed on the patient cohort treating the duration of storage as the continuous variable that it is. One way of doing this would be to **develop a "total storage duration exposure" for each patient** by summation of the numbers of storage days of each transfused unit. This would **allow the 2364 patients who received both newer and older blood to be included in the analysis**. Since this study is retrospective, it would be **inappropriate to interpret its conclusions as necessitating a change in current transfusion practices**. Therefore they suggest performing the suggested further analysis in order to validate or refute the study's conclusions.

6. ***Editors' Note***: in addition to the suggestions of colleagues submitted so far, the Editors believe that the NEJM report **would benefit** from an analysis **comparing the outcomes** of patients who **only received leukocyte-reduced red cells** and to compare the outcomes of those patients against patients who **received one or more red cell units that were not leukocyte reduced**.

ADDENDA April 22, 2008

7. **A transfusion medicine physician specializing in pediatrics** agrees with the comments already posted in this discussion. Additionally, he would add that **another problem with the NEJM article's retrospective analysis** is that it **covered an 8 year period** from June 30, 1998 to January 30, 2006. Conceivably, **operative and peri- operative care improved during this time period** while **RBC units tended to get fresher** (or universally leukocyte reduced) at the same time. RBC units would have tended to get fresher if there were larger RBC inventories at the beginning of the study time period and tighter inventories towards the end of the study period. Two factors that impacted RBC inventories during the study time period were the attacks on Sept. 11, 2001 and changing donor deferral criteria for European travel. Other factors could have also impacted their RBC inventories. If these confounders caused the average age of transfused RBCs to decrease while clinical care improved, the study would have found improved outcomes with fresher RBC units. ***Editors' note***: In the article "Transfusion in Coronary Artery Bypass Grafting is Associated with Reduced Long-Term Survival" by Koch et al, (the lead author of the NEJM article) it is pointed out that **universal leukocyte reduction was instituted at the Cleveland Clinic in 2002**. However, since the NEJM article report spans June 30, 1998 to January 30, 2006, the introduction of universal leukocyte reduction **might add yet another potential confounder** which could make outcomes appear better with fresher blood, if clinical care improved over the study period.

At the responding colleague's pediatric hospital they had **already been providing fresher RBC units for 'young' surgical patients but not for older surgical patients**. This has been driven by concerns of transfusion associated hyperkalemia, which is more of a risk in very young patients. While the responding colleague **reports no plans to change** their local inventory management, **anesthesiologists have voiced concerns in response to the NEJM**

article and **meetings to discuss these concerns are planned**.

ADDENDA May 2, 2008

8. ***Editors' Note***: A Federal Register Notice has been posted announcing the Meeting of the Advisory Committee on Blood Safety and Availability on May 29-30, 2008. **Of particular note**: The Committee will be asked to **discuss and make recommendations** on reports of adverse outcomes associated with transfusion of older red cells.

ADDENDA June 2, 2008

9. ***Editors' Note***: A representative from the Biomedical Excellence for Safer Transfusions (BEST) Collaborative has posted a press release, noting key inadequacies of recent studies on red blood cell age and encouraging analyses of other data.

ADDENDA June 13, 2008

10. ***Editor's Note***: The presentation made to the US Dept of HHS Advisory Committee on Blood Safety & Availability by Larry Dumont, MBA, PhD for the Biomedical Excellence for Safer Transfusion (BEST) Collaborative may be viewed on the BEST website HERE.

ADDENDA June 28, 2008

11. **Dr. Priscilla Figueroa, co-author of the NEJM paper and transfusion service medical director at the Cleveland Clinic** (attribution used with permission) reports that since there is so much interest in the Cleveland Clinic's NEJM paper, colleagues may want to know that the Cleveland Clinic does not specifically provide fresh units for its cardiac surgery patients. **Their cardiac surgeons were informed that the blood bank would not be changing transfusion policies until the results of prospective studies were available**. In regard to Neil Blumberg's question (see ADDENDA Mar. 31, 2008), the Cleveland Clinic's blood inventory is **essentially 100% leukocyte reduced**. Dr. Figueroa acknowledges that the only time they may have nonleukocyte reduced units is during times of shortages when they may be forced to import units from an organization other than their regular provider.

Please submit comments to the e-Network Forum.

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Addenda: Mar. 28, 30 & 31, April 4, 15 & 22, May 2, June 2, 13 & 28, 2008