Peer Review File
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Reviewer A

Comment 1: The cost of transfusion is very well described but the cost of alternative therapies to reduce transfusion is not. It would be nice to describe the cost of each drug that is recommended (for example: the cost of iron injection, ESA, TXA, cell salvage....). Describing the cost of these therapies will highlight the advantage of the PBM program over the cost of transfusion. It is important to convey that the PBM program is beneficial to the patient and the institution. In this study, this message is not clear because the cost of the PBM program is not described.
Reply 1: We agree that costs should be explored for alternative therapies.
Changes in the text: Costs added to alternative therapies.

Comment 2: This study describes the cost of transfusion and possible options for limiting the use of transfusion. Many PBM guidelines, which are not cited in this study, describe the strategy to reduce the risk of transfusion with a level of evidence for each recommendation. It would be valuable to include these references and their recommendations in this review.
Reply 2: We agree that references should be updated to include some of these valuable studies.
Changes in the text: References updated to include PBM studies.

Comment 3: To assess the cost of transfusion, the ABC (activity-based costing) method described by Shander et al for transfusion is sometimes used. Methods for calculating the total cost of transfusion are not discussed in this review. It is important to develop and review this issue.
Reply 3: Thank you for bringing this to our attention. The author of the section included a method.
Changes in the text: Method added to calculate overall cost of a unit of blood.

Comment 4: The first section "Overview of Blood Products" does not bring particular interest to this review if the reader is a transfusing physician. There is no link with the cost of transfusion.
Reply 4: We agree that this may not be of interest to a transfusing physician, but the audience is not specific to transfusing clinicians. We want to appeal to a broad audience, including general practitioners who may not know the difference between certain blood products. We think this is an important addition to the paper.
Changes in the text: Title changed to Blood Component Overview. Section shortened to include only red blood cells.

Comment 5: Table 3 describes the cost of RBC transfusion. This table highlights the wide variability between countries, but no explanation is offered to understand this difference. It is important to clarify whether these prices are for the same type of RBC product? Are these the average or median prices? Do you have any ideas to explain these differences? It would be nice to add an additional column to specify all prices in dollars or euros to better compare prices.
Reply 5: Author agrees that table should be clearer and specify currency to more inclusive.
Changes in the text: Exchange rate included for USD and EU currency. Disclaimer added on inflation. Author also contributed to discussion in body of text.

Comment 6: The formulas for calculating the total cost of RBC transfusion are not described
Reply 6: Please see comment three as well.
Changes in the text: Formulas for calculating the total cost of RBC transfusion is further explained.

Comment 7: In the section "preoperative hemoglobin optimization" no information is described regarding iron deficiency even though it is the leading cause of anemia. Information regarding iron deficiency and ESAs, described in L419-437, should be moved to this section. Based on the guidelines, dosing should also be offered.
Reply 7: Authors agree on adding more information on IDA and ESAs.
Changes in the text: Information on both subjects added in appropriate sections.

Comment 8: L388: Tranexamic acid (TXA) is described as an alternative therapy. It is important to note that this therapy is widely recommended in all the surgeries that have the potentiel to bleed, not just for orthopaedic surgery, trauma, or postpartum bleeding (e.g., cardiac surgery...)
Reply 8: Section author recognized importance of adding diversity to TXA use.
Changes in the text: TXA use expanded to include more than orthopedic surgery.

Comment 9: Prothrombin complex concentrate (PCC), vitamin K, and fibrinogen are not alternative therapies to TXA. The use of PCC is recommended for urgent correction of coagulopathy due to vitamin K antagonists, especially if there is a risk of volume overload. Fibrinogen concentrates are indicated for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency or to reduce dilutional coagulopathies. These treatments are recommended in very specific situations compared to TXA which is recommended pre emptively for all bleeding surgeries.
Reply 9: Authors agree with reviewer A.
Changes in the text: PCCs removed as an alternative to TXA

Comment 10: The “associated costs” section foes not contribute to the discussion.
Reply 10: Associated cost section did not contribute. Section was reformatted to better outline costs and discussion.
Changes in the text: Section removed and costs added elsewhere within text.

Reviewer B

Comment 1: Under blood product overview, the sentence “whole blood is collected from donors and processed through various means to create individual blood products” should state “blood components”. Red blood cells, plasma, platelets, and cryoprecipitate are blood components.
Reply 1: Authors agree
Changes in the text: Section changed to blood components and terminology updated throughout when referencing components.

Comment 2: Under blood product overview, there is a discussion on preparation of plasma, platelets and cryoprecipitate. However, the Reimbursement for Transfusion discussion that follows primarily deals with the costs associated with red blood cell transfusions. My recommendation is

to take out the information on other blood components and concentrate on red blood cells. This will also shorten the article.
Reply 2: The authors believe that all blood products should be included in PBM strategies and contribute to cost. We do agree with the reviewer that red cells do make up a larger portion of reimbursement, however.
Changes in the text: Component preparation removed from section.

Comment 3: Under reimbursement for transfusion, there is very detailed discussion of costing that is specific to the American blood system. This detailed discussion may be of interest to health economists but would be less valuable to the general audience. Please consider condensing. On the other hand, I appreciated the fulsome discussion of various itemized costs associated with transfusion of a unit of red blood cell; the discussion of these types of costs is universally applicable and interesting.
Reply 3: The authors agree with the reviewer on condensing this section.
Changes in the text: Section condensed, paragraphs deleted and information condensed.

Comment 4: Under modalities of patient blood management, I disagree with a statement that the PBM program exists mainly through transfusion practice committee. This committee plays a very important role in patient blood management but other important entities include preoperative patient blood management clinics, education, etc. and these have not been mentioned.
Reply 4: Authors agree that the statement should be more inclusive, it was not intentionally written in that way.
Changes in the text: Updated section to be more inclusive of PBM program members.

Comment 5: Under modification of transfusion behavior, there is a sentence that "since the advent of blood transfusion, the risks associated with transfusion have only increased throughout the years with newer technology". I disagree with this statement. We may have become aware of more risks over the years but the overall risk of transfusion has decreased significantly. For example, the risk of acquiring HIV through blood transfusion has dropped exponentially with advent of new technology. There is no doubt, that RBC transfusion n ow is safer than it was 20 years ago.
Reply 5: The authors intent with this statement was that there are more transfusion reaction categories and causes than when transfusion first started. As we continue to study blood, we learn more about adverse effects from transfusion and its contribution to morbidity and mortality.
Changes in the text: Section updated to remove that phrasing.

Comment 6: Under modalities of PBM, since your discussion concentrates mainly on the costs associated with RBC transfusion, it would make sense to discuss PBM modalities most relevant to reduction of RBC transfusion - cell salvage, tranexamic acid, iron and erythropoiesis stimulating agents. Use of ESA in pre-operative patients is highly relevant but not included. Under modalities of PBM, I would opt to omit discussion on PCC, vitamin K as well as fibrinogen concentrate. These are not broadly applicable and instead are used in specific circumstances to manage bleeding risk.
Reply 6: Authors agree
Changes in the text: Section omitted and ESA discussion added.

Comment 7: I was disappointed to see no discussion of the costs associated with cell salvage,

TXA, iron and erythropoiesis stimulating agents. Since the point of the article is to discuss the economics of patient blood management, it is also imperative to include at least some information on the relative costs of these modalities – and perhaps even compare/contrast with the cost of RBC. I also saw no discussion about costs of pre-operative or rapid anemia clinics or multi-modal large-scale PBM programs. There was only discussion of cost savings linked to CPOE and audits as well as inventory management strategies. This is not sufficient to appreciate the full picture of PBM vs transfusion economics.
Reply 7: Authors agree that anemia clinicals and or multi-modal PBM programs should be included.
Changes in the text: Anemia clinics and PBM models were included in a cost analysis section as well as in their own pre-operative/rapid anemia clinic section.

Reviewer C

Comment: Authors have addressed an interesting issue. Patient Blood Management is a strongly recommended strategy by many scientific societies of surgery and anesthesiology. If many studies have demonstrated interesting results on sparing blood products, no study has considered the impact on economics of PBM implementation. The possible reason is that the topic is rather complex. The authors give an exhaustive catalog of the various techniques and alternatives that are proposed in the PBM strategy. The reader would like to have more data on costs of these techniques and alternatives. As a matter of fact, it is surprising that there is no much numeric data when addressing economics. Moreover, the title suggests that some comparison, namely with or without PBM, would support the discussion development. As it stands, the manuscript is more descriptive of what PBM consists in, than demonstrative on economic impact.
Reply: The authors agree with the statement that more numerical data should be included.
Changes in Text: More numerical data is included and costs analyses are included. These elaborate on the costs associated with transfusion, alternative therapies, and prevention clinics. We have even standardized some of the costs to control for inflation during the time of the study and provided a break down in different currencies.

Reviewer D

Comment: The review "Economics of Patient Blood Management in the Unites States" is well written. The authors describe in detail costs associated with the preparation of blood products, reimbursement of blood transfusion and modalities of PBM. However, I have one major concern, which should be addressed before publication. The title of the review is misleading. Economics of PBM is poorly described. Several cost analyses have been performed for the described PBM modalities and should be mentioned in this review.
Reply: The authors agree and this aligns with multiple other comments from other reviewers.
Changes in Text: Cost-analyses have been added and put in their own section in the manuscript.