Yen *Clinical and Translational Gastroenterology* (2018)9:150
DOI 10.1038/s41424-018-0019-2

Clinical and Translational Gastroenterology

EDITORIAL Open Access

Blood transfusion strategies for acute upper gastrointestinal bleeding: are we back where we started?

Andrew W. Yen, MD, FACG, FASGE[1]

Abstract

Blood transfusion practices for acute upper gastrointestinal hemorrhage have changed over time. Restrictive strategies, which gave way to more liberal approaches for the greater part of the 20th century, have again gained traction as emerging research suggests restricting transfusion is associated with similar, or possibly better outcomes in UGI bleeding. In a large, retrospective cohort study from an integrated health care system in Taiwan, Chen, et al., report the association between early blood transfusion and clinical outcomes in patients presenting to the emergency department with UGI bleeding, and these findings are discussed in the context of current knowledge and practice.

We shall not cease from exploration

And the end of all our exploring

Will be to arrive where we started

And know the place for the first time.

-T.S. Eliot

Allogeneic blood transfusion as a form of routine medical therapy started in the early part of the 20th century. For some patients, such as those with rapid blood loss from traumatic or obstetrical injuries, transfusions were lifesaving[1,2]. Early reports of transfusion in patients with exsanguinating gastrointestinal bleeding also supported and expanded the practice beyond the operating room[3]. But from an early stage, thresholds for transfusion in GI bleeding remained unsettled as observations of rebleeding after transfusion led to initial recommendations to withhold blood at the onset of hemorrhage, with judicious administration based on a patient's clinical condition[4].

In the decades that followed, however, transfusing blood for anemic patients became one of the most widely utilized medical therapies[5], often driven by anxiety toward any level of anemia, regardless of etiology. At the time, the rationale for transfusion seemed obvious—low blood counts could lead to poor tissue perfusion, organ failure, and death, so avoidance of anemia appeared intuitive and more liberal strategies to correct it were adopted. The practice of transfusing when hemoglobin levels fell below 8–10 g/dL, an arbitrary trigger proposed in a 1942 report[6], was subsequently generalized broadly to surgical and non-surgical conditions, and persisted in some guidelines, including those for acute UGI bleeding[7], into the early 21st century. For decades, transfusion enjoyed a privileged status as a 'grandfathered' therapeutic, not requiring broader evidence or rigorous scientific scrutiny.

In the 1980s and 1990s, discovery of hepatitis C, the HIV epidemic, and a confluence of factors highlighted growing concerns about the safety of blood products and raised consideration for limiting transfusions. In 1999,

Correspondence: Andrew W. Yen (andrew.yen3@va.gov)
[1]Division of Gastroenterology, Sacramento VA Medical Center, Veterans Affairs Northern California Health Care System (VANCHCS), University of California Davis School of Medicine, Sacramento, USA

Hébert, et al.[8], published a large randomized controlled trial of 838 critically ill patients in the intensive care unit assigned to one of two groups: those receiving a transfusion if their hemoglobin fell below 10 g/dL, and those receiving a transfusion if their hemoglobin fell below 7 g/dL. There was no difference in 30-day mortality. Gastrointestinal diseases, however, comprised only a small portion of the study population.

In the subsequent years, at least 7 additional large, RCTs evaluating patients with a variety of surgical and non-surgical conditions were published[9–15], each comparing restrictive transfusion strategies to liberal ones. In all of these, patients fared as well as, or sometimes better, with a restricted approach. However, only two of these RCTs focused on patients with acute UGI hemorrhage[12,15].

The first, a single-center, unblinded European study[12], randomized 921 patients with acute UGI bleeding of any etiology to a restrictive (<7 g/dL) or liberal (<9 g/dL) strategy. Patients with exsanguinating bleeding and cardiac ischemia were excluded. The restrictive group had significantly lower 45-day mortality and rebleeding. The positive effects of restriction appeared more pronounced in those with chronic liver disease and portal hypertension, and notably, all patients received urgent endoscopy, <6 h from presentation, which may have impacted outcomes.

A multicenter cluster-randomized pilot feasibility study of liberal vs. restrictive transfusions in a UK population across six hospitals followed[15]. Nine hundred thirty-six patients with UGI bleeding of any etiology were randomly assigned to receive transfusion at a hemoglobin <8 vs. <10 g/dL. Patients with exsanguinating hemorrhage were excluded as well. There was no significant difference between treatment arms for 28-day mortality or further bleeding, although this trial was not powered to assess clinical outcomes.

These data provided support for updated transfusion recommendations for UGI bleeding[16,17], but the need for additional study was clear. In this edition of Clinical and Translational Gastroenterology, Chen, et al.[18], report the findings of a large, retrospective observational cohort study exploring the association between red blood cell transfusion, administered within 24 h of emergency department presentation, and mortality in patients with acute UGI bleeding of any etiology, in a large health care system in Taiwan over a 10-year period. Data from six institutions were abstracted for analysis from a centralized, comprehensive database using ICD-9 coding and clinical information stored in the electronic medical record. A total of 59,188 patients were included in the study, which allowed for robust statistical analyses using logistic regression modeling, propensity matching, and sensitivity and survival analyses.

In all unadjusted and adjusted models, (early) transfusion was significantly and consistently associated with higher rates of mortality and rebleeding. In subgroup analysis, patients with cirrhosis (HR 0.73, 95% CI 0.68–0.83, $p < 0.001$) (Child Pugh A or B) and those with variceal hemorrhage (HR 0.78, 95% CI 0.62–0.81, $p < 0.001$) appeared to benefit most from avoidance of transfusion. Although observations based on a retrospective analysis raise the possibility of bias toward transfused patients being sicker at baseline, the authors attempt to adjust for multiple patient and treatment related factors, thereby providing additional insights into the potential influence of important variables including ischemic heart disease, cerebral vascular accidents, hemorrhagic shock, cirrhosis, anithrombotic use, early (<24 h) endoscopy, and need for hemostatic therapy. Although the authors rely on coding to collect much of the data, the analysis of this very large cohort provides important associations between transfusion and clinical outcomes for patients treated in a large, integrated health system.

Even though nearly 40% of the study population did not ultimately require hospital admission from the emergency department, and therefore, did not have the primary outcome of mortality tracked, all patients in the cohort underwent risk stratification by endoscopy, which presumably provided important prognostic information that influenced admission and treatment decisions. A sizable cohort of hospitalized patients (30,342) remained for survival analysis. Additional points to note include the timing of endoscopy, which was dichotomized to early (<24 h from presentation) or late (>24 h), but not further subdivided to determine if urgency of endoscopy played a significant role in administration of transfusion, and thus outcomes, an area of interest raised by an earlier RCT[12]. Additionally, transfusion was defined as blood received within the first 24 h of presentation. If transfusion was provided outside this range during the course of treatment, it was not counted. It is unclear how often this occurred. Although early transfusion was also associated with increased rates of rebleeding in this study, conclusions on hemoglobin targets for transfusion cannot be clearly drawn.

Based on this study and the two preceding RCTs[12,15], restricting transfusion appears to be as good as, or potentially better than a liberal approach, in acute UGI bleeding, particularly in patients with portal hypertension. But many questions remain, including the optimal trigger for transfusion; the significance of early vs. late transfusion or volume transfused; the importance of endoscopy timing; and the influences of ongoing bleeding, administration of other transfused products, and comorbid conditions.

The reason why transfusion worsens outcomes in some also remains unclear. The theory that transfusion increases portal and/or systemic pressures, thereby promoting further bleeding, may have merit, but is likely an oversimplification. Other variables including impairment

of coagulation, changes incurred in the stiffness of stored red blood cell membranes, transient inability of transfused RBCs to effectively deliver oxygen to end organs (due to depleted 2,3-diphosphoglycerate), decreased functional capillary density, additional known and unknown effects of blood storage, antigen-mediated immune reactions, and paradoxical dampening of the immune response may also play important roles[19–21].

But among the growing chorus for limiting transfusions, it is still important to avoid the assumption that a liberal strategy is by itself harmful. Clearly, in some patients with rapid blood loss, transfusion remains lifesaving[22], but exsanguinating bleeding may represent a distinct condition and hemorrhagic shock may trigger a different set of physiologic processes and responses that requires unique treatments[23,24]. However, the line between how much or rapid the blood loss to necessitate replacement is unknown and likely influenced by a complex interplay of factors including patient specific comorbidities, such as ischemic heart disease, traumatic brain injury, and risk factors for brain or spinal cord ischemia, conditions that not infrequently coexist in patients with GI bleeding. Ischemic heart disease alone was present in 20.9% of those presenting with UGI bleeding in one series[25].

Nevertheless, for the majority of patients presenting with UGI bleeding without evidence of ischemia, a restrictive transfusion strategy appears to be associated with better outcomes. Specific hemoglobin cut-offs as recommended by current guidelines appear reasonable, but should still be approached with discretion since hemoglobin is not a good proxy for tissue oxygenation, particularly in the setting of acute blood loss, and absolute values should be viewed as an imperfect parameter for transfusion decisions. Broad adherence to restrictive practices must respect individual patient conditions, as interpreted by a comprehensive review and assessment of the complexities of individual comorbidities and risk factors, requiring physicians to exercise clinical judgment when deciding whether or not to transfuse—recommendations that echo the sentiments from the early 20th century, when transfusions emerged as a novel therapeutic. But now, in the 21st century, we have more objectivity and guidance behind these recommendations, a greater understanding of the limitations of the available evidence, and deeper insight into the questions that still need to be answered about transfusion in UGI bleeding.

Conflict of interest

Guarantor of the article: Andrew W. Yen, MD, FACG, FASGE
Specific author contributions: Andrew W. Yen: Reviewed initial study; performed literature search; drafted editorial and approved final submission.
Financial support: None
Potential competing interests: None

Received: 25 February 2018 Accepted: 27 February 2018
Published online: 25 April 2018

References

1. Primrose, A. & Ryerson, E. S. The direct transfusion of blood: its value in haemorrage and shock in the treatment of the wounded in war. *Br. Med. J.* **2**, 384–386 (1916).
2. Luker, S. G. Case of recurrent haemorrhage from laceration of the cervix, treated by blood transfusion and hysterectomy. *Proc. R. Soc. Med.* **13**, 161–163 (1920).
3. Eads, J. T. Massive gastrointestinal hemorrhage. *J. Am. Med. Assoc.* **131**, 891–893 (1946).
4. Pollard, H. M. & Wollum, A. Role of transfusions in the management of gastric hemorrhage. *J. Am. Med. Assoc.* **145**, 22–26 (1951).
5. Facts and Figures 2009—Section 3 Table of Contents. Healthcare Cost and Utilization Project (HCUP).2012. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/reports/factsandfigures/2009/section3_TOC.jsp.
6. Adams, R. C. & Lundy, J. S. Anesthesia in cases of poor surgical risk: some suggestions for decreasing the risk. *Surg. Gynecol. Obstet.* **74**, 1011–1019 (1942).
7. Non-variceal upper gastrointestinal haemorrhage: guidelines. British Society of Gastroenterology Endoscopy Committee. *Gut* **51**, iv1–iv6 (2002).
8. Hébert, P. C., Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N. Engl. J. Med* **340**, 409–417 (1999). Erratum in: N Engl J Med 1999 Apr 1;340(13):1056.
9. Lacroix, J., Pediatric Acute Lung Injury and Sepsis Investigators Network. et al. Transfusion strategies for patients in pediatric intensive care units. *N. Engl. J. Med.* **356**, 1609–1619 (2007).
10. Hajjar, L. A. et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA* **304**, 1559–1567 (2010).
11. Carson, J. L., FOCUS Investigators. et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N. Engl. J. Med.* **365**, 2453–2462 (2011).
12. Villanueva, C. et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N. Engl. J. Med.* **368**, 11–21 (2013).
13. Holst, L. B., Scandinavian Critical Care Trials Group. et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N. Engl. J. Med.* **371**, 1381–1391 (2014).
14. Carson, J. L. et al. Liberal versus restrictive blood transfusion strategy: 3-year survival and cause of death results from the FOCUS randomised controlled trial. *Lancet* **385**, 1183–1189 (2015).
15. Jairath, V. et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. *Lancet* **386**, 137–144 (2015).
16. Barkun, A. N., International Consensus Upper Gastrointestinal Bleeding Conference Group. et al. International consensus recommendations on the management of patients with nonvaricealupper gastrointestinal bleeding. *Ann. Intern. Med.* **152**, 101–113 (2010).
17. Laine, L. & Jensen, D. M. Management of patients with ulcer bleeding. *Am. J. Gastroenterol.* **107**, 345–360 (2012).
18. Chen Y. C., Hsiao C. T., Lin L. C., Hsia K. Y., Hung M. S. The association between red blood cell transfusion and outcomes in patients with upper gastrointestinal bleeding. *Clin. Transl. Gastroenterol.* **9**, 138 (2018).
19. Tsai, A. G., Cabrales, P. & Intaglietta, M. Microvascular perfusion upon exchange transfusion with stored red blood cells in normovolemic anemic conditions. *Transfusion* **44**, 1626–1634 (2004).
20. Zimrin, A. B. & Hess, J. R. Current issues relating to the transfusion of stored red blood cells. *Vox. Sang.* **96**, 93–103 (2009).
21. Shander, A. et al. A new perspective on best transfusion practices. *Blood Transfus.* **11**, 193–202 (2013).
22. Perel, P. et al. PROGRESS Partnership. Red blood cell transfusion and mortality in trauma patients: risk-stratified analysis of an observational study. *PLoS. Med.* **11**, e1001664 (2014).
23. Spinella, P. C. & Cap, A. P. Whole blood: back to the future. *Curr. Opin. Hematol.* **23**, 536–542 (2016).
24. Cannon, J. W. Hemorrhagic Shock. *N. Engl. J. Med.* **378**, 370–379 (2018).
25. Hearnshaw, S. A. et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* **60**, 1327–1335 (2011).