Blood Transfusion for Gastrointestinal Bleeding

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Gastrointestinal bleeding accounts for more than 450,000 hospitalizations annually in the United States[1] and is a frequent indication for red-cell transfusion. Blood transfusions are given to 43% of patients hospitalized with upper gastrointestinal bleeding in the United Kingdom[2] and to 21% of patients hospitalized with lower gastrointestinal bleeding in the United States.[3]

Transfusion practices for patients with gastrointestinal bleeding have fluctuated over the past 100 years. Avoidance of transfusions early in the 20th century, owing to concern that increased blood pressure would induce rebleeding, gave way to more liberal use of transfusions,[4] and a hemoglobin threshold for transfusion of 10 g per deciliter was recommended up to the early 2000s.[5] On the basis of more recent data, current guidelines for the management of gastrointestinal bleeding have returned to a restrictive transfusion strategy, recommending a hemoglobin threshold of 7 g per deciliter.[6,7] Meta-analyses of randomized trials of restrictive transfusion thresholds as compared with liberal transfusion thresholds show no significant differences in 30-day mortality, length of hospital stay, or rates of adverse events and largely exclude the possibility of a clinical benefit with a liberal transfusion strategy.[8,9] However, only 0 to 1% of the patients in these analyses had acute gastrointestinal bleeding, which raises concerns about the generalizability of these results to patients with gastrointestinal bleeding.

The important study by Villanueva et al. in this issue of the *Journal*[10] provides long-awaited evidence to guide practice and justify current recommendations for the management of upper gastrointestinal bleeding. A hemoglobin threshold for transfusion of 7 g per deciliter, as compared with a threshold of 9 g per deciliter, was associated with a significant 45% relative-risk reduction in 45-day mortality. On the basis of the results of this study, 25 patients would have to be treated according to a restrictive transfusion strategy rather than a liberal transfusion strategy to avert one additional death at 45 days. The decrease in mortality was accounted for primarily by fewer deaths from bleeding that could not be successfully controlled. Significant reductions with the restrictive strategy were also seen in the rates of further bleeding, transfusion reactions, and cardiac events and in the length of hospital stay.

Largely on the basis of results from studies in animals, a restrictive transfusion strategy is commonly used for patients with variceal bleeding to prevent rebound increases in portal pressure, and Villanueva et al. suggest that the benefit of the restrictive transfusion strategy was seen mainly in patients with portal hypertension. However, subgroup analyses performed by the authors do not support a conclusion that the benefit differed between patients with and those without portal hypertension. No formal test of interaction was provided, but hazard ratios for further bleeding and for death were similar in the overall group and in subgroups with cirrhosis, esophageal varices, or peptic ulcer, with closely overlapping confidence intervals.

Although the results of the study by Villanueva et al. apply to a broad group of patients with upper gastrointestinal bleeding, modification of the transfusion threshold may be considered in specific subpopulations, such as patients with hypotension due to severe bleeding and patients with cardiovascular disease. Hemoglobin values early in the course of acute bleeding are minimally decreased and, in patients with substantial intravascular volume depletion, markedly overestimate the "true" hemoglobin level that will be seen after fluid resuscitation and equilibration. Approximately 30% of the patients in the study by Villanueva et al. had "hypovolemic shock," defined as a systolic blood pressure of <100 mm Hg and a heart rate of >100 beats per minute). Multivariable analysis showed that a restrictive transfusion strategy significantly decreased further bleeding, even after adjustment of the analysis for hypovolemic shock. However, the analysis of mortality was not adjusted for hypovolemic shock, results were not provided for patients with more marked hypotension (e.g., systolic blood pressure <80 or 90 mm Hg), and patients with massive bleeding were excluded from the study. Until more data are available, it may be reasonable to give transfusions to patients with marked hypotension due to bleeding before

the hemoglobin reaches 7 g per deciliter in order to forestall the drop to levels well below 7 g per deciliter that would occur with fluid resuscitation alone.

There is also uncertainty regarding the need for a higher transfusion threshold in patients with cardiovascular disease, and evidence is available from populations without gastrointestinal bleeding. Subgroup analyses of data from patients with cardiovascular disease in two previous large, randomized trials of a restrictive transfusion strategy as compared with a liberal transfusion strategy revealed no increased risk with restrictive hemoglobin thresholds of 7 g per deciliter and 8 g per deciliter.[11,12] Current guidelines recommend considering transfusion when the hemoglobin level falls to 8 g per deciliter or when cardiovascular symptoms develop in hemodynamically stable patients with preexisting cardiovascular disease.[9]

A final question is whether a restrictive transfusion strategy has attributes that provide benefit for patients with gastrointestinal bleeding beyond that seen in other populations. Randomized trials involving patients without gastrointestinal bleeding have not shown significant improvements in most clinically important outcomes with a restrictive transfusion strategy as compared with a liberal transfusion strategy.[8,9] In contrast, the study by Villanueva et al. shows superiority in key outcomes, such as bleeding and mortality.[10] Lower splanchnic blood flow or pressure and less impairment in coagulation may explain, at least in part, the significant reductions in bleeding and bleeding-related deaths seen with a restrictive transfusion strategy in patients with gastrointestinal bleeding.

In conclusion, the study by Villanueva et al. provides important evidence to guide clinical practice. Most patients with upper gastrointestinal bleeding, with or without portal hypertension, should have blood transfusions withheld until the hemoglobin level drops below 7 g per deciliter.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Polycythemia Vera, the Hematocrit, and Blood-Volume Physiology

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Marchioli et al.[1] report in the *Journal* that a hematocrit target of less than 45% for therapeutic phlebotomy reduces the risk of thrombosis in patients with polycythemia vera. In the genomic era, readers may question attention given to a measurement as mundane as the hematocrit, but this study resolves a half-century of debate about the role of phlebotomy in polycythemia vera and has ramifications for diagnosis and management.

Polycythemia vera is a unique myeloproliferative disorder in which there is overproduction of morphologically normal erythrocytes, granulo-