# Clinical decision support and improved blood use in patient blood management

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**Despite many years of published medical society guidelines for red blood cell (RBC) transfusion therapy, along with clinical trials that provide Level 1 evidence that restrictive transfusion practices can be used safely and are equivalent to transfusions given more liberally, annualized blood transfusion activity did not begin to decline in the United States until 2010. Adoption of electronic medical records has subsequently allowed implementation of clinical decision support (CDS): best practice alerts that can be initiated to improve the use of blood components. We describe our own institutional experience using a targeted CDS to promote restrictive blood transfusion practice and to improve RBC use. A 42% reduction in RBC transfusions was demonstrated at our institution from a baseline in 2008 through 2015, and the rate remained stable through 2018. Although the data cannot be used to infer causality, this decreased RBC use was accompanied by improved clinical outcomes.**

**Learning Objectives**

- Understand how CDS can improve use of blood components
- Know that a reduction in inappropriate RBC transfusions is associated with improved clinical outcomes

## Clinical case

A 64-year-old woman presented to the emergency department with hematemesis. On presentation, she had a systolic blood pressure of 70 mm Hg and heart rate of 140 beats per minute (bpm). Her hemoglobin (Hb) concentration was 6 g/dL. She received 2 L of crystalloid fluids and was transfused with 3 units of packed red blood cells (RBCs). Emergent upper endoscopy revealed a bleeding gastric peptic ulcer that was clipped. She was transferred to the intensive care unit where she was evaluated by the on-call medicine intern. She denied any current chest pain, shortness of breath, lightheadedness, dizziness, or hematemesis. Her blood pressure was now 130/80 mm Hg and her heart rate was 80 bpm. Her Hb was 8.1 g/dL. Unaware of evidence suggesting that a restrictive transfusion strategy would be appropriate in the setting of acute upper gastrointestinal bleeding, the admitting intern ordered a transfusion of 1 unit of packed RBCs. How can clinical decision support (CDS) reduce such inappropriate transfusions?

## Introduction

The American Board of Internal Medicine has identified blood transfusion as the most frequent and overused therapeutic intervention in the United States.[1] To curtail inappropriate transfusions, accreditation agencies such as The Joint Commission have proposed performance indicators in patient blood management (PBM) to promote restrictive transfusion practices.[2] However, physicians historically have not adhered to clinical practice guidelines,[3] including those recommending prudent transfusion practices,[4] as evidenced by their ineffectiveness in improving RBC use in the United States over a 20-year interval (1988-2009). Beginning in 2011, RBC transfusions in adult hospitalized patients in the United States have decreased annually.[5]

The case for RBC transfusions being issued inappropriately can perhaps best be illustrated by the persistent variability in RBC use in patients undergoing coronary artery bypass surgery in the United States, first demonstrated in 1991 with a study that involved 18 institutions[6] and was subsequently corroborated by the Society for Thoracic Surgeons national database, in which continued variability in RBC use was not accompanied by any differences in clinical patient outcomes.[7] Such variability exposes patients to the risks of RBC transfusion therapy without receiving any benefit.

Given that outside the situation of acute hemorrhage, we do not have clear evidence for the efficacy of RBC transfusion, and RBC transfusions are possibly harmful in the long term[8]; the guiding principle for RBC transfusion therapy is now "less is more." Recent recommendations from the American Society of Hematology[9] and the American Association of Blood Banks[10] advocate that RBC transfusions be administered as single units (one at a time) for nonbleeding hospitalized patients. This key concept was first proposed more than 35 years ago, based on posttransfusion risks known at that time as non-A, non-B hepatitis, so that a 1-unit RBC transfusion was therefore arithmetically safer than a 2-unit transfusion. The American College of Physicians was the first medical society to recommend that after the initial RBC unit was transfused, additional units should be prescribed only after the patient had been reassessed.[11] Promoting single-unit RBC transfusions may have an even greater impact on RBC use than simply promoting restrictive transfusion practices.[12]

## Restrictive transfusion

PBM describes the proactive multidisciplinary and collaborative strategies for delivering patient health care with a goal of improved

Conflict-of-interest disclosure: L.T.G. and M.A.H. declare no competing financial interests.

Off-label drug use: None disclosed.

use of transfusion therapies, and with a goal of minimizing or even eliminating their use. Restrictive transfusion practice is a key element of PBM, incorporating the principle of giving RBC transfusions only when the potential benefits are deemed to outweigh potential risks, along with a goal of minimizing the use of RBC units.[2] Improving blood safety and promoting restrictive blood transfusion practices first gained impetus in the 1980s in response to the recognition that hepatitis C virus and HIV were transmitted by blood transfusion.[4] Since then, despite substantial advances in safety with respect to infections transmitted by transfusion, evidence has accumulated to indicate that RBC transfusion continues to be associated with other short- and long-term adverse patient outcomes. Institutional experience and national databases indicate that a restrictive RBC transfusion approach and other measures to minimize the use of RBC transfusion, such as detection and management of preoperative anemia,[2] began to have an impact as best practices when RBC transfusions began to decline annually in the United States starting in 2010.[4]

Although the risks of transfusing RBCs are known and can be quantified, the short-term benefits are less certain and not easily quantifiable. A 2016 Cochrane meta-analysis of 32 trials in more than 12 000 patients compared restrictive transfusion to liberal RBC transfusion strategies.[13] Patients randomly assigned to restrictive transfusions were 43% less likely to receive an RBC transfusion. The risk of dying within 30 days of the RBC transfusion (primary outcome) was the same whether the participants received RBCs at lower or higher Hb levels.

Randomized controlled trials in a variety of clinical settings now provide Level 1 evidence for restrictive transfusion practices. Three noninferiority trials in adults in intensive care units,[14] cardiothoracic surgery postoperatively,[15] or repair of hip fracture postoperatively[16] found that patients could tolerate a restrictive RBC transfusion strategy with Hb concentrations as low as 7 to 8 g/dL. Clinical outcomes (mortality rates) in patients treated with a restrictive RBC transfusion strategy were equivalent to those in patients transfused to maintain concentrations >10 g/dL. A fourth study[17] in adults with upper gastrointestinal bleeding found that a more restrictive RBC transfusion practice (transfusion when Hb was <7 g/dL) had improved re-bleeding rates and 45-day mortality when compared with patients transfused to maintain Hb concentration >9 g/dL. A fifth trial[18] in children in critical care found that a threshold of 7 g/dL was safe in patients who were hemodynamically stable. Two additional trials[19,20] in cardiothoracic patients demonstrated restricted transfusion practices (Hb as low as 7.5 g/dL) to be noninferior to liberal strategies.[21]

Although evidence from meta-analyses and these 7 trials is persuasive, there remains some uncertainty.[22] For example, the evidence from controlled trials of transfusions for anemia in critical care patients with heart disease or acute coronary syndromes is less robust. A multicenter trial of 110 patients with acute coronary syndromes who were randomly assigned to receive RBC transfusions at Hb <8 g/dL or 10 g/dL found that the liberal transfusion strategy was associated with a lower mortality rate but with similar rates of myocardial infarction or unscheduled coronary artery bypass surgery.[23] A more liberal RBC transfusion strategy in the management of anemia may therefore be warranted in patients at risk such as the elderly[24] or those with acute coronary syndromes.[25]

Although some have called for an absolute defined Hb threshold for RBC transfusion based on these trials, it is critical that clinical judgment be incorporated into RBC transfusion decisions, taking into account patient risk factors and comorbidities.[26] Increasing evidence shows that RBC transfusions are poorly effective in the immediate term and possibly harmful in the long term.[8] Most guidelines agree that transfusion should not take place when the Hb level is >10 g/dL but may be considered at concentrations <7 to 8 g/dL.[4]

## CDS

A variety of different strategies have been attempted with the goal of reducing inappropriate transfusion practices. Before the widespread implementation of electronic medical record (EMR) systems, these efforts included institutional guidelines, educational programs, physician audit of transfusion orders, and paper order forms that outlined criteria for audits of RBC transfusions. Such interventions have generally been ineffective in reducing the use of transfusions. Moreover, interpretation of data has been limited by publication bias (interventions are more likely to be published if they were effective) and bias resulting from before-and-after study design.

The broad implementation of EMR systems made it possible to offer tailored feedback (education) to the provider at the time of physician

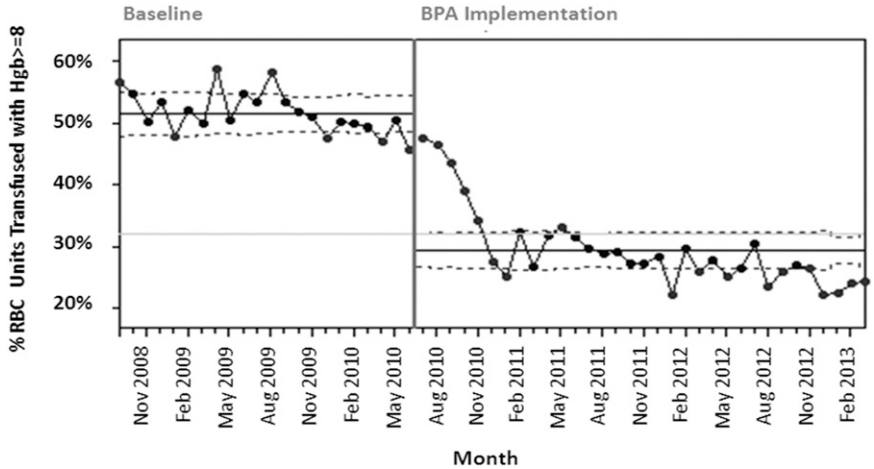


**Figure 1.** The percentage of stable (non-bleeding) patients transfused with RBCs whose last recorded Hb level was >8 g/dL from November 2008 through February 2013. Patients in procedural units (operating room, cardiac catheterization laboratory) were excluded, as were patients with a diagnosis of hemorrhage in the discharge problem list.[31]

order entry (POE) as a new approach to reducing inappropriate use.[27] Such electronic CDS systems provide the advantage over previous approaches of lower investment of time for the transfusion service physicians, complete standardization, and the ability to automatically collect large amounts of data. A review of CDS studies published since 2000[28] identified barriers to the successful implementation of CDS: ordering provider time constraints, economic constraints, lack of knowledge of systems or content, reluctance to use the system in front of patients, obscure workflow issues, unreliability of information, and lack of consensus among physicians or users toward the system. Nevertheless, hospitals with EMR systems can and should implement CDS. The costs associated with CDS are small compared with the total cost associated with EMRs, and costs from CDS can be recovered via cost savings from improved use of RBCs.

We implemented a CDS initiative in July 2010 for RBC transfusions, in which a smart best practice alert (BPA) is triggered when a provider orders RBCs for patients whose pretransfusion Hb was above an Hb threshold (7 g/dL or 8 g/dL for patients with acute coronary syndrome or postcardiothoracic procedure).[29] The process and method for implementation of smart BPA at the time of POE has been described previously.[30]

The alert provided a reminder that single-unit RBC transfusions are usually preferable,[11] along with the most recent laboratory results for Hb concentration for the patient. In addition, there was an "acknowledgment reason" dropdown query that required the ordering physician to provide an answer to why the RBC transfusion was ordered: Hb value, bleeding, or other. However, it is important to note that our selection of an Hb threshold was intended to trigger a concurrent use review by the ordering physician of their decision to order an RBC transfusion, rather than providing a suggested trigger for RBC transfusion.[26] Subsequent to our implementation of the BPA for RBCs in July 2010, the percentage of RBC transfusions in patients whose pretransfusion Hb was >8 g/dL decreased from 60% beforehand to 35% in the 6 months after implementation[2] and then to less than 30% (Figure 1).[31]

Overall, there was a reduction in RBC transfusions by 42% from 2008 through 2015 when analyzed as RBC units transfused per number of patient-days at risk.[29] As detailed in Table 1, a significant decrease was found before implementation of our BPA (18.3 RBC units per 100 days at risk in 2009) compared with after implementation (14.0 RBC units per 100 days at risk in 2010). There was a continued, significant trend downward from 2011 through 2015.[32] The decreased use has continued at this level through 2018, with transfusions of 11.7, 11.0, and 10.9 RBC units per 100 days at risk for 2016, 2017, and 2018, respectively (Figure 2).[21] During this interval, hospital-wide mortality for all patients decreased significantly, whereas other patient clinical outcomes including 30-day re-admission rates remained stable. The improvement in patient outcomes (mortality, length of stay, and 30-day re-admission rate) was even more demonstrable when only the hospitalized patients who actually received RBC transfusions were analyzed (Table 2).[31] This improvement in patient outcomes cannot be assumed to be causal; however, it is reassuring that there was no demonstrable increase in adverse patient outcomes with our hospital-wide adoption of restrictive RBC transfusion practices. This observation has also been reported in an analysis by others,[33] in which there was no evidence that patients who were managed with restrictive RBC transfusion practices were undertransfused.

**Table 1. Blood components transfused and patient outcomes: 2008-2018**

| Parameters | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patient activity** | | | | | | | | | | | |
| No. of RBC transfusions | 29 331 | 28 855 | 24 860 | 22 727 | 22 725 | 22 772 | 24 421 | 23 712 | 26 599 | 24 777 | 24 924 |
| No. of plasma transfusions | 14 871 | 12 970 | 12 811 | 10 300 | 10 108 | 9 722 | 10 193 | 9 237 | 9 160 | 8 015 | 8 143 |
| No. of platelet transfusions | 7 880 | 8 412 | 8 355 | 8 286 | 7 398 | 8 052 | 9 906 | 9 218 | 9 846 | 8 792 | 9 629 |
| No. of patient-days at risk* | 156 374 | 165 153 | 180 652 | 186 004 | 197 855 | 201 908 | 211 558 | 220 906 | 226 051 | 224 955 | 228 179 |
| Case mix index | 1.95 | 1.98 | 1.95 | 2.02 | 2.03 | 2.07 | 2.23 | 2.28 | 2.41 | 2.47 | 2.47 |
| No. of RBC units per 100 days at risk | 18.8 (± 1.3) | 18.3 (± 1.8) | 14.0 (± 1.4) | 12.4 (± 0.8) | 11.6 (± 0.8) | 11.5 (± 0.8) | 11.7 (± 0.7) | 10.7 (± 0.8) | 11.7 (NA) | 11.0 (NA) | 10.9 (NA) |
| **Patient outcomes** | | | | | | | | | | | |
| Mortality | 2.83 | 2.81 | 2.59 | 2.53 | 2.55 | 2.44 | 2.59 | 2.41 | 2.75 | 2.67 | 2.56 |
| 30-day re-admissions | 10.4 | 10.7 | 11.5 | 11.0 | 10.6 | 10.4 | 10.6 | 10.8 | 10.9 | 11.1 | 11.0 |
| LOS, d (IQR) | 3 (2-6) | 3 (2-6) | 3 (2-6) | 3 (2-6) | 3 (2-6) | 3 (2-6) | 3 (2-6) | 3 (2-6) | 3 (2-6) | 3 (2-6) | 3 (2-6) |

This table has been updated from previously published analyses.[30] Values are mean (± standard deviation) if available, except 30-day re-admission, mortality rates (per 100 discharges), and length of stay (LOS), which is represented as median (interquartile range [IQR]). Mortality rates decreased significantly ($P < .0002$) from 2008 to 2015 and remained stable through 2018.
NA, not applicable.
*Patient-days at risk takes into account both number of discharges and LOS. There was a 42% reduction in RBC units per 100 patient-days at risk from 2009 to 2015, remaining stable thereafter through 2018.

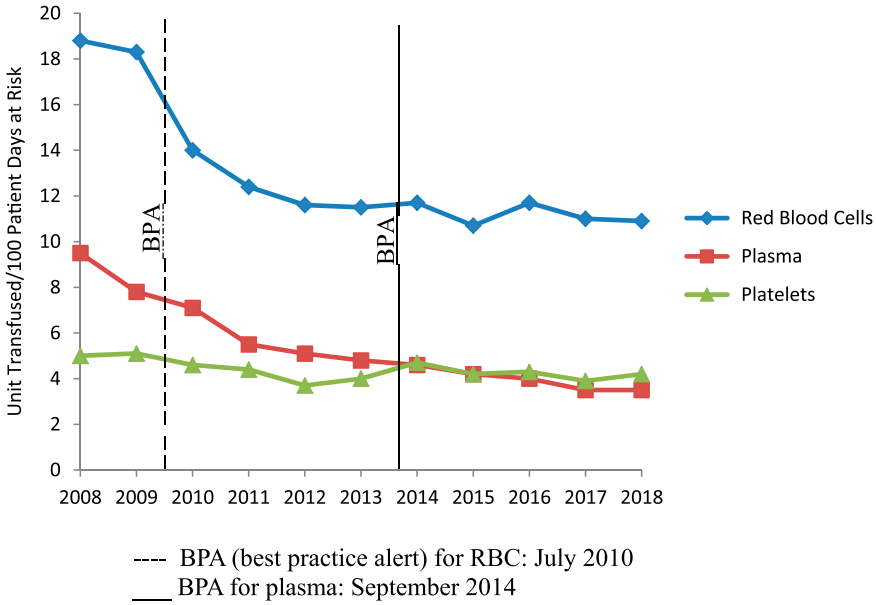


**Figure 2.** Trends in blood component use at Stanford Health Care, 2008-2018. The abscissa shows data for the end of each year.

In an analysis of medical facilities with nearly 400 000 inpatients in Kaiser Permanente Northern California from 2009 to 2013, the incidence of RBC transfusions decreased from 14% to 10.8% of all admissions, with a decline in pretransfusion Hb levels from 8.1 to 7.6 g/dL, but 30-day mortality did not change significantly over this same time interval.[34] A follow-up report found that increased anemia after hospitalization was not accompanied by a rise in subsequent RBC use, prehospitalization, or mortality within 6 months of hospital discharge.[35]

Additional benefits of our CDS initiative have included a savings of an estimated $1.6 million annually in purchase costs for RBC units.[29] Purchase or acquisition costs represent only a fraction of the total costs of RBC transfusion; an activity-based cost summary of RBC transfusions demonstrated savings of up to 5 times the purchase costs. Hence, the estimated total transfusion-related savings exceeded $35 million over a 6-year period, in the context of improved patient safety from reduced exposures to allogeneic RBC transfusions. Blood components (RBC, plasma, and platelets) transfused at our institution from 2008 to 2018 are illustrated in Figure 2. There was a reduction in plasma units per 100 days at risk, likely in part because of a BPA implementation in 2014 for plasma orders.[36] This reduction in plasma use continued through 2018, with 4.0, 3.5, and 3.5 plasma units transfused per 100 days at risk for 2016, 2017, and 2018 compared with 4.8 and 4.2 for 2014 and 2015, respectively.

## Clinical case continued

Upon entering an order for RBC transfusion, the intern received an interruptive BPA, which stated that "Strong evidence suggests that in hemodynamically stable, non-bleeding patients, an Hb threshold of 7 g/dL (or 8 g/dL in acute coronary syndromes after cardiac surgery) can decrease transfusion requirements and avoid adverse outcomes." There was an option to remove the transfusion order or proceed with the order if clinically indicated. The intern reviewed the case with his senior resident, which prompted a discussion of the evidence that a restrictive transfusion strategy (transfusion when Hb level is <7 g/dL) significantly improved outcomes in patients with acute upper GI bleeding when compared with a liberal strategy (transfusion when Hb level is <9 g/dL).[17] The intern removed the transfusion order. The patient remained hemodynamically stable and did not require any further RBC transfusions.

## Challenges and future directions: what our patient clinical experience has highlighted

Despite the successes of CDS in reducing inappropriate transfusions, several important challenges and limitations of this approach remain. This is highlighted by the fact that up to 25% of RBC transfusions at our institution still occur in patients with a pretransfusion Hb level >8 g/dL.

During 2011-2012, 98% of BPAs were overridden at our institution by the ordering provider.[37] This finding is consistent with observations by others that providers are reluctant to cancel orders on the basis of BPA, especially when no alternative order is suggested to them by the EMR system.[38] In many cases, the BPA is overridden appropriately. Situations in which the BPA is appropriately overridden include acute hemorrhage and patient populations in

**Table 2. Demographic profile and clinical outcomes in stable patients transfused with RBCs**

| Variables | Pre-BPA | Post-BPA | *P* |
|---|---|---|---|
| No. of patients | 3622 | 10 528 | |
| Age, y | 59.7 ± 17.4 | 59.8 ± 17 | .76 |
| % Female | 54.3 | 50.2 | .0001 |
| Case mix index | 2.78 | 2.86 | .0001 |
| RBC units transfused | 3.6 ± 4.1 | 2.7 ± 3.0 | .0001 |
| Length of stay, d | 10.1 ± 13.3 | 6.2 ± 10.2 | .0001 |
| % Mortality | 5.5 | 3.3 | .0001 |
| % 30-day readmission | 13.7 | 8.5 | .0001 |
| Discharge Hb, g/dL | 9.9 | 9.0 | .0001 |

Values are mean (± standard deviation) if available. Procedural areas (eg, operating room, cardiac catheterization laboratory) were excluded along with patients who had discharge diagnoses or problem lists that include hemorrhage.[31]

which a modified transfusion trigger for stable patients may be appropriate.[37] Such patient populations include neonates, those with cardiovascular risk factors or active acute coronary syndromes, the elderly, and postpartum patients.[24,39] However, a significant portion of overrides do not seem to be based on evidence-based rationales for RBC transfusion. We hypothesize that one important reason for the reluctance to cancel transfusion orders is that those who place the orders lack authority. Most of the ordering providers for transfusions at our institution are residents and registered nurses (who generally place orders either per verbal order from the physician or as part of a transfusion protocol). Attending physicians only rarely place RBC transfusion orders, and therefore are unlikely to benefit from the educational aspect of the BPA. Another reason for the routine override of the BPA are RBC transfusion practices that are part of a set protocol, most commonly on subspecialty services such as hematology, oncology, and stem cell transplant units, in which routine transfusion of RBCs at Hb thresholds above 7.0 g/dL is the norm.[37] These data suggest that further interventions may need to be targeted not only toward ordering providers through CDS but via educational initiatives outside the EMR system. These could include institutional RBC transfusion guidelines that are disseminated to attending physicians in addition to those who regularly place orders in the EMR (trainees, advanced practice providers, and registered nurses).

We found that at our institution, a number of services routinely transfuse patients for Hb values >7.0 g/dL when there is no evidence for or against this practice. For example, our stem cell transplant service routinely transfuses patients for an Hb level >8.0 g/dL. For these situations, further evidence from large randomized clinical trials is necessary to determine whether the benefits of transfusion outweigh the risks. In contrast, some services routinely transfuse patients for indications in which evidence suggests that risks outweigh benefits, such as surgical services that routinely transfuse stable patients before their procedure.[37] Here, there is need for further education and collaboration between surgeons and transfusion medicine specialists to develop evidence-based RBC transfusion protocols.

Given the high rate of BPA override that we have observed, another critical factor to consider is alert fatigue. One study showed that the likelihood of accepting a BPA dropped by 30% for each additional reminder received per encounter.[40] Our clinicians receive large numbers of BPAs, including those related to medication interactions, allergies, and appropriate laboratory ordering practices. Therefore, it is important to weigh the risks and benefits of each BPA that is added to such a system. There is a real risk that the transfusion BPA will lead to a provider over-riding a BPA that could have a life-threatening consequence, such as giving a patient a medication that they have a documented anaphylactic response to. Further research is needed to quantify such risks. Going forward, it will be important to consider ways that the POE system can be tailored to each subspecialty or even each clinician to maximize the benefit and minimize the risk of BPAs.

In conclusion, implementation of real-time CDS correlates with reduction of inappropriate blood transfusions and their related costs. Clinical patient outcomes either improve or remain stable concurrent with improved blood use. These observations provide assurance that restrictive transfusion practices can be successfully implemented institution-wide without causing patient harm.

## Correspondence

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