CME

Current Status of Pharmacologic Therapies in Patient Blood Management

Lawrence Tim Goodnough, MD* and Aryeh Shander, MD†

Patient blood management[1,2] incorporates patient-centered, evidence-based medical and surgical approaches to improve patient outcomes by relying on the patient's own (autologous) blood rather than allogeneic blood. Particular attention is paid to preemptive measures such as anemia management. The emphasis on the approaches being "patient-centered" is to distinguish them from previous approaches in transfusion medicine, which have been "product-centered" and focused on blood risks, costs, and inventory concerns rather than on patient outcomes. Patient blood management[3] structures its goals by avoiding blood transfusion[4] with effective use of alternatives to allogeneic blood transfusion.[5] These alternatives include autologous blood procurement, preoperative autologous blood donation, acute normovolemic hemodilution, and intra/postoperative red blood cell (RBC) salvage and reinfusion. Reviewed here are the available pharmacologic tools for anemia and blood management: erythropoiesis-stimulating agents (ESAs), iron therapy, hemostatic agents, and potentially, artificial oxygen carriers. (Anesth Analg 2013;116:15–34)

Patient blood management is a multiprofessional (physicians, nurses, perfusionists, pharmacists) and multidisciplinary (e.g., transfusion medicine specialists, surgeons, anesthesiologists, and critical care specialists) approach that is hospital-wide and patient-centered[6] on management of anemia, perioperative blood conservation and surgical hemostasis, and blood use. Professional societies such as the Society for the Advancement of Blood Management,[1,7] the American Association of Blood Banks,[8] and the Network for Advancement of Transfusion Alternatives,[9] as well as hospital accreditation organizations such as the Joint Commission[10] and Department of Human Health Services,[11] have each developed initiatives in patient blood management.

ESAs, recombinant activated Factor VII (rFVIIa), hemostatic agents, (e.g., aprotinin), parenteral iron therapy, and artificial oxygen carriers have each undergone reevaluation regarding their relative benefits and risks as potential alternatives to allogeneic blood transfusion. In this review, we summarize the current roles of these pharmaceutical interventions in patient blood management.

From the *Pathology Department, Stanford University, Stanford, California; and †Department of Anesthesiology, Critical Care Medicine, Pain Management, and Hyperbaric Medicine, Englewood Hospital and Medical Center, Englewood, New Jersey.

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Address correspondence to Lawrence Tim Goodnough, MD, Pathology Department, Stanford University, 300 Pasteur Drive Room H-1402, M/C 5626 Stanford, CA 94305. Address e-mail to ltgoodno@stanford.edu.

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ERYTHROPOIESIS-STIMULATING AGENTS

The current status for approval of ESAs is summarized in Table 1.[12] ESAs have been approved in patients undergoing elective surgery[12,13] and in oncology patients with chemotherapy-induced anemia, based on prospective randomized trials that demonstrated reduced allogeneic blood transfusion in patients receiving such therapy.[14–16] ESAs were first demonstrated and approved for use to increase the hemoglobin (Hgb) levels in patients with end-stage chronic kidney disease (CKD) undergoing dialysis[17] and without dialysis[18]. Before the introduction of ESAs, dialysis patients with CKD commonly required blood transfusion support and its associated complications with significant morbidity[19] such as iron overload.[20] Since 1992, approximately 90% of patients undergoing dialysis in the United States are now managed with ESA therapy to address anemia of CKD.[21] Similarly, in a Cochrane review[22] for oncology patients, transfusion requirements in this setting have also been significantly reduced with ESA therapy, for a relative risk reduction observed (relative risk = 0.64; 95% confidence interval, 0.60–0.68).

Subsequent to Food and Drug Administration (FDA) approval for the use of ESA to reduce allogeneic blood transfusion in these clinical settings, clinical trials were undertaken in an attempt to further demonstrate long-term improved patient outcomes with ESA therapy (Table 2).[23–36] In elective surgery patients scheduled for elective spine surgery, blood transfusion and patient outcomes were compared for ESA and placebo-treated cohorts. These patients did not receive anticoagulation prophylaxis for thrombotic adverse events (in contrast to the clinical trials in joint replacement patients that resulted in approval for the use of ESAs in elective surgery). This study

Table 1. Erythropoiesis Stimulating Agents: Current Approval Status

	Perisurgical	PAD	ESKD Predialysis/dialysis	CIA
Japan	No	Yes (1993)	Yes (1990, 1994)	No
European Union	No	Yes (1994)	Yes (1988, 1990)	Yes (1994)
United States	Yes (1996)	No	Yes (1989, 1990)	Yes (1993)
Canada	Yes (1996)	Yes (1996)	Yes (1990, 1990)	Yes (1995)

PAD = Preoperative autologous donation; ESKD = end-stage kidney disease, predialysis/dialysis; CIA = chemotherapy-induced anemia.
Updated from Goodnough et al.[12]

documented a higher incidence of deep vein thrombosis in patients receiving epoetin alfa compared with placebo. However, the rates of clinically relevant deep vein thrombosis and other thrombovascular events were similar between the treatment groups and well within published rates for this population. The authors concluded that antithrombotic prophylaxis should be considered when ESAs are used in surgical patients, including those who undergo elective spine surgery. Accordingly, the prescribing information for these agents was modified in the label on the basis of these findings.

The investigations in CKD[24–29] and oncology[30,31,33–37] patients focused on whether targeting or maintaining Hgb levels within normal or at the upper range of normal could benefit patients by improving patient survival. However, more "aggressive" anemia management in these trials was associated with increased morbidity (thrombosis or cardiovascular events) or increased mortality in the ESA-treated cohorts. In patients with end-stage CKD (estimated glomerular filtration rate < 60 cm^3/min per 1.73 $m)^2$ and Hgb < 12 g/dL), ESA treatment was associated with an increased risk of acute stroke, with the greatest effect among patients who also had a diagnosis of cancer.[38] The risks of death or cardiovascular events were associated with a poor initial hematopoietic response, as doses of ESAs were escalated to meet target Hgb levels.[28]

Literature reviews and meta-analyses of ESA trials for both approved and off-label oncology settings have studied survival and other safety outcomes.[22,32,39–45] One of these indicated that for Phase III controlled trials of ESA therapy (chemotherapy, radiotherapy, and anemia of cancer patients),[42] mortality was higher in the ESA cohorts compared with the placebo cohorts (hazard ratio 1.10; confidence interval, 1.01–1.20; $P = 0.03$). Overall, 3 meta-analyses[41,42,44] indicated increased risk of mortality with use of ESA, whereas two[43,45] indicated that ESA did not significantly affect mortality. The mechanisms behind any ESA-associated increase in morbidity and mortality outcomes are unclear. One hypothesis is that ESAs stimulate disease progression and/or thrombosis by activating erythropoietin receptors (EPO-Rs) present in tumor cells or associated vascular endothelium.[46]

In a follow-up retrospective analysis of EPO-R expression in tumor samples from patients in the Erythropoeitin in Head and Neck Cancer Study (ENHANCE),[43] locoregional progression-free survival was decreased in patients treated with ESAs only in the subpopulation of patients whose tumors expressed EPO-R,[47] suggesting a potential direct

Table 2. Postapproval Clinical Trials of ESA

Patients' trial	Target vs. control (Hgb)	Reference (y)	Clinical outcomes
I. Surgery			
Spine	<13	Stowell et al., 2009[23]	Inc Thrombosis
II. Chronic kidney disease			
A. Dialysis	≥13 vs 10	Besarab et al.,1998[24]	Dec OS
B. Predialysis			
CHOIR	13.5 vs 11.3	Singh et al., 2006[25]	Dec OS
CREATE	13–15 vs 10.5–11.5	Drüeke et al., 2006[26]	Dec OS
TREAT	13 vs 9	Pfeffer 2006[27–29]	Dec OS
III. Oncology			
A. Chemotherapy			
Lymphoma	≥ 14–15 (F,M)	Hedenus et al., 2003[30]	Dec OS
Breast (BEST)	>14	Leyland-Jones et al., 2005[31]	Dec OS
Breast (PREPARE)	≥13	Untch et al., 2011[32]	Inc Thrombosis
B. Radiotherapy			
Head/neck (ENHANCE)	≥14–15 (F,M)	Henke et al., 2003[43]	Dec OS
Head/neck (DAHANCA)	>15.5	Overgaard et al., 2007[33]	Dec DFS
Chemo/radiotherapy (Gynecologic oncology group)	>14	Thomas et al., 2008[34]	Dec OS
C. No/palliative therapy			
Nonsmall cell lung	≥14	Wright et al., 2007[35]	Dec OS
Nonmyeloid cancer	≥13	Smith et al., 2008[36]	Dec OS

ESA = erythropoiesis-stimulating agents; Inc = increased; Dec = decreased; OS = overall survival; DFS = disease-free survival; CHOIR = Correction of Hemoglobin and Outcomes in Renal; CREATE = Cardiovascular Risk Reduction by Early Treatment with Epoetin beta; TREAT = Trial to Reduce Cardiovascular Events with Aranesp Therapy; BEST = Breast Cancer Erythropoietin Survival; ENHANCE = Erythropoeitin in Head and Neck Cancer Study; DHANCA = Danish Head and Neck Cancer Group; PREPARE = Preoperative Epirubicin Paclitaxel Aranesp Study.

tumor effect of ESA therapy on tumor progression; however, the antibody used to detect EPO-Rs in tumors lacks specificity.[48,49] EPO-R mRNA levels vary as much as 30-fold among breast cancer and head and neck cancer specimens and vary between tumor epithelial and endothelial cell fractions. Solid tumors can be segregated by their overall EPO-R levels,[50] suggesting known heterogeneity in tumor vasculature. Other investigators, however, have found no evidence that EPO-R is functionally expressed in tumors[51] or is present in nonhematopoietic cells.[52]

In a meta-analysis of Phase III trials that reported survival and venous thromboembolism outcomes, 52 trials with 13,611 patients and 38 trials with 8172 patients, respectively, were analyzed by comparing ESAs with placebo or standard of care for the treatment of anemia among patients with cancer.[41] Patients who received ESAs had increased risks of venous thromboembolism (7.5% vs. 4.9%; relative risk, 1.57 [1.31–1.87]) and increased risk of mortality (hazard ratio, 1.10 [1.01–1.20]). These findings, coupled with the 8 clinical trials in oncology patients that followed patients for clinical outcomes when ESA therapy was designed to sustain or achieve Hgb levels within the normal range, raised concerns about the safety of ESA administration to patients with cancer. Whether recommended Hgb levels are beneficial for survival independent of reduced exposure to allogeneic blood transfusions is the subject of ongoing clinical studies.

FDA approval of ESAs in cancer patients with chemotherapy-induced anemia continues to be based on their demonstrated benefit of reducing/avoiding the need for RBC transfusions (and not other possible benefits such as improved quality of life). Based on the above evidence, the labeling for use of ESAs in perisurgical, CKD, and oncology settings has been modified to reflect guideline updates,[53,54] black box warnings, and FDA-mandated risk evaluation and mitigation strategies by treating physicians that include patient educational materials and cautionary text in consent forms. The revised labels also reflect safety concerns regarding target Hgb levels > 12 gm/dL. Similar black box warnings based on safety concerns have been inserted into the labels for use of ESAs in patients with end-stage kidney disease and in patients undergoing elective surgery.[55] The black box warnings and updated guidelines remind treating physicians that the use of ESAs should be based on the initiation of therapy in patients whose Hgb levels are <10 g/dL or who have symptomatic anemia; and to target minimal ESA dosage toward RBC responses sufficient for patients to benefit from ESA therapy by avoidance of or reduced allogeneic blood transfusions.

One concern has been that if ESA use is reduced significantly, then the rate of RBC transfusions in patients will increase in these settings. After the National Coverage Decision in July 2007, effects of reimbursement changes on ESA use were found in oncology patients aged 65 years and older; that is, a 31% increase in transfusions was observed.[56] Similarly, recent evidence from the U.S. Renal Data System for the first 9 months of 2011 suggests that the share of patients covered by Medicare who received blood transfusions increased by 9% to 22% over the corresponding months in 2010.[57] These data suggest that more stringent Hgb levels, coupled with payer restrictions such as the National Coverage Decision dialysis rule changes, have also been associated with increased blood transfusions in dialysis patients. The prospect of increased RBC transfusion rates should be taken seriously, given the large body of evidence linking blood transfusions with potentially untoward patient outcomes as well as the negative and potentially destabilizing effect of the increased demand on blood inventory. It should be noted that the data indicate a <10% margin between the total numbers of blood units collected and transfused in the United States.[58] These observations have led to concerns that controversies over use of ESA therapy as an alternative to RBC transfusion will inflict collateral damage to the blood supply.[59] In clinical practice, the increased risks of death and thromboembolic events should be balanced against the benefits of treatment with ESAs, considering each patient's clinical circumstances and preferences.[60] The approved dosage for epoetin alfa in oncology patients is 600 units/kg at weekly intervals for 4 weeks.

IV IRON THERAPY

The relationship between erythropoietin, iron, and erythropoiesis and the presence of iron-restricted erythropoiesis has important implications in anemia management. Iron-restricted erythropoiesis can occur in the following: absolute iron deficiency, functional iron deficiency, and/or iron sequestration (Fig. 1).[61] Absolute iron deficiency is common in women, children, and the elderly. Functional iron deficiency occurs in patients with

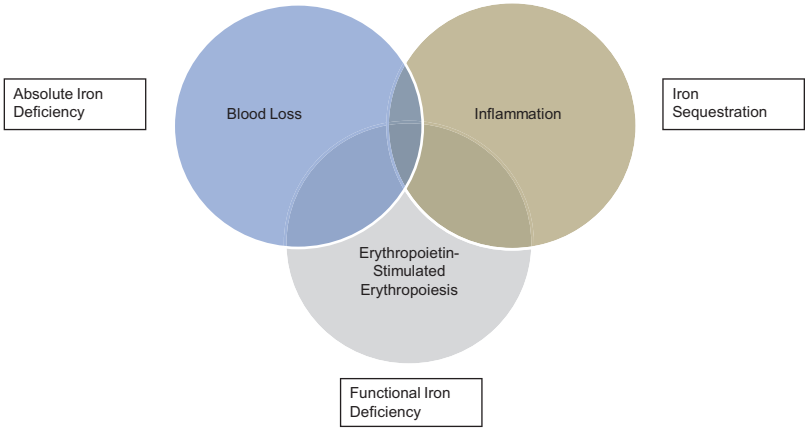

Figure 1. Iron deficiency syndromes. The relationships between absolute iron deficiency, iron sequestration, and functional iron deficiency are illustrated. Patients can have ≥1 combinations that all result in iron-restricted erythropoiesis. Adapted from Goodnough LT.[61]

significant erythropoietin-mediated erythropoiesis or ESA therapy, even when storage iron is present. Iron sequestration, mediated by hepcidin, is an underappreciated but common cause of iron-restricted erythropoiesis in patients with inflammation.

Conditions contributing to the development of absolute iron deficiency have been reviewed.[62] Blood loss is a major cause of iron deficiency (e.g., female patients with menses, patients with chronic occult gastrointestinal blood loss, and community blood donors) and is important not only because of its prevalence but also because proper diagnosis and management of the bleeding lesion are important.[63–65] Therapeutic management is primarily focused on repletion of iron stores. Most iron-deficient individuals without inflammation respond well to oral iron therapy, but administration of IV iron may be beneficial in patients with inflammation.[66–69]

The development of functional iron deficiency (in which increased demand for iron by the erythron exceeds rates of mobilization of iron from storage) in healthy subjects[61] is observed by a reduction in transferrin saturation (TSAT) within 1 week of initiation of ESA therapy. The decrease in TSAT is also demonstrated in patients undergoing aggressive autologous blood donation, with or without ESA therapy.[70] A decline in serum ferritin also occurs, reflecting shift of iron from storage pools into newly synthesized Hgb.[71] An enhanced RBC production is seen in response to parenteral iron therapy in CKD patients treated with ESA therapy, demonstrating that this functional iron deficiency can be ameliorated with IV iron therapy with increases in serum iron and TSAT.[72]

While sequestration of iron has long been known to be central to the pathogenesis of the anemia of chronic disease,[73] understanding of the regulation of iron homeostasis has changed substantially in the last 10 years.[74–77] Hepcidin is a small peptide hormone secreted mainly by hepatocytes and has emerged as the central regulator of iron absorption, and plasma iron levels. Hepcidin production is strongly increased by inflammation and infection. Hepcidin exerts its effect by binding and degrading the iron exporter, ferroportin,[76] thus reducing the iron available for erythropoiesis.[77] Hepcidin acts to sequester iron by inhibiting storage iron egress from hepatocytes and macrophages into plasma, and also inhibits absorption of dietary iron from duodenal enterocytes.

The development of a sensitive, accurate, and reproducible immunoassay for human hepcidin has allowed definition of physiologic and pathologic changes of hepcidin in healthy volunteers and in patients.[78] The assays will be useful in improving our understanding of the pathogenic role of hepcidin in various iron disorders, and in the development of appropriate therapeutic interventions. In contrast to changes in ferritin levels, changes in hepcidin concentrations are the cause of, rather than the result of, iron disorders. Hepcidin antagonists may be an effective treatment for patients with inflammatory anemia.[79]

The diagnostic and therapeutic implications for considerations in iron-restricted erythropoiesis depend on the assessment of whether the patient has absolute iron deficiency, an iron sequestration syndrome, and/or functional iron deficiency. Traditional biochemical assays including serum iron, total iron-binding capacity, iron saturation percentage, and serum ferritin are not always helpful in evaluating the iron status in patients with inflammation.[67] An algorithm for anesthesiologists' evaluation of preoperative anemia in patients scheduled for elective surgery has been developed and published by a consortium of European Societies, in which the algorithm is centered on an evaluation for iron-restricted erythropoiesis.[80]

Expected changes in iron variables in various clinical conditions, and in the potential use of hepcidin assays for hepcidin-targeted therapies and iron therapies in patients with various forms of anemia, are summarized in Table 3.[61,67,81] As the pathogenic mediator of inflammation, hepcidin would be expected to be high in iron sequestration syndromes. It is noteworthy that hepcidin levels are reliably elevated in patients with anemia of inflammation (AI) compared with normal values, and are low or undetectable in patients with absolute iron deficiency. However, in patients who have mixed problems, AI coexisting with absolute iron deficiency, or functional iron deficiency, hepcidin levels alone may not reliably distinguish among iron deficiency syndromes.[82,83] Because hepcidin levels are affected by iron stores, this assay may also identify patients most likely to respond to iron therapy or identify patients at risk for iron loading.[78]

Even under the best of circumstances, oral iron is not well tolerated, and patients are often nonadherent.[84] In addition, hepcidin response in inflammatory conditions inhibits gastrointestinal absorption of oral iron. While evidence in rodents suggests that in the presence of both iron deficiency and inflammation, hepcidin levels are more responsive to the erythropoietic demands for iron than to inflammation

Table 3. Potential Role of Iron Therapy in Management of Anemia

Condition	Expected hepcidin levels	Iron parameters	Iron therapy strategies	Potential hepcidin therapy
Absolute iron deficiency anemia (IDA)	Low	Low Tsat and ferritin	Orally or IV if poorly tolerated or malabsorbed	No
Functional iron deficiency (ESA therapy, CKD)	Variable, depending on ± CKD	Low Tsat, variable ferritin	IV	Antagonist (if hepcidin levels not low)
Iron sequestration (anemia of inflammation[AI],	High	Low Tsat, normal-to-elevated ferritin	IV	Antagonist
mixed anemia [AI/IDA, or AI/functional iron deficiency anemia)	Variable	Low Tsat, low-to-normal ferritin	IV[a]	Antagonist (if hepcidin levels not low)

Tsat = transferrin saturation;CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent.
[a]Mixed anemia is a diagnosis of exclusion without a therapeutic trial of iron.
Adapted from Goodnough LT.[61]

and that oral iron can be absorbed,[67] oncology patients respond better to IV iron therapy than to oral iron supplementation in chemotherapy-induced anemias treated with ESA.[68,85–87] Despite these beneficial effects, IV iron administration may generate oxidative stress and other inflammatory changes. Long-term effects of the IV iron preparations will require careful study in relevant clinical settings.[88,89]

Therapy with ESAs in management of the anemia of chronic renal failure has led to substantial clinical experience in supplemental IV iron therapy in this setting.[73,90] Hyporesponsiveness to ESA therapy is a common phenomenon[91,92] attributable to a variety of comorbid conditions, but is particularly related to functional iron deficiency.[70,71] Patients with anemia undergoing dialysis may show suboptimal or no response to oral iron therapy for several reasons. During ESA therapy, although absorption of iron can increase up to 5-fold[93] presumably as a result of hepcidin suppression by increased erythropoiesis, continuing external iron losses as a result of hemodialysis and blood testing can exceed the intake.[94,95] Furthermore, some patients have poor compliance with iron therapy or significantly reduced gastrointestinal iron absorption. Absorption of oral iron can be enhanced with ascorbate by at least 30%, because it reduces ferric iron to ferrous iron.[95] Iron absorption and release from stores may be impaired because of high hepcidin levels from diminished clearance by the kidneys not completely corrected by routine hemodialysis, as well as from inflammation. Indeed, overexpression of hepcidin in mice blocked the hematopoietic response even to large doses of ESA.[74]

IV iron administration has been successful in renal dialysis patients undergoing ESA therapy[96] and is recommended for management of anemia by the National Kidney Foundation Guidelines.[97] Patients treated with IV iron (100 mg twice weekly) achieved a 46% reduction in ESA dosage required to maintain hematocrit levels between 30% and 34%, compared with patients supplemented with oral iron.[98] To further address the management of iron-restricted erythropoiesis in CKD patients undergoing dialysis, a randomized, controlled trial evaluated the effectiveness of IV iron supplementation in patients with ferritin levels between 500 ng/mL and 1200 ng/mL.[99] The administration of IV iron (and increasing the dose of ESA by 25%) resulted in a greater correction of anemia compared with increasing the dose of ESA alone. After the end of the trial, there was greater success in reducing the dose of ESA in the patients receiving IV iron, compared with the non iron-treated arm.

In patients with malignancy and chemotherapy-induced anemia, clinical trials have studied IV iron in the setting of therapy with ESAs. In one study[85] of patients undergoing chemotherapy, 155 patients were treated with ESA and were randomized to receive no iron, oral iron, or IV iron. There were significant improvements in Hgb levels and hematopoietic responses in both patient groups treated with IV iron, compared with those receiving oral iron or no iron therapy.

Iron-restricted erythropoiesis has been shown to be a consideration at the time of cancer diagnosis, even before initiation of ESA therapy: 17% of patients were found to have serum ferritins <100 ng/mL and 59% had TSAT <20% at diagnosis.[37] In addition, renewed attention has been placed on the relationship between ESA dose and RBC production responses in ESA-treated patients.[100] Recent controversies regarding the safety of ESA therapy in patients with malignancies and chemotherapy-induced anemia[101] have led to the development of guidelines by the American Society of Hematology/American Society of Clinical Oncology[53] and the National Comprehensive Cancer Network[54] that recommend iron studies be obtained at baseline to identify patients who are candidates for supplemental iron therapy; and that if subsequent Hgb levels after 4 weeks of ESA therapy indicate no response (<1 g/dL increase in Hgb), then IV iron supplemental therapy should be considered, along with an increase in ESA dose.

IV iron therapy also improved responses to ESA therapy in patients with inflammatory bowel disease compared with responses in a similar patient group who receive oral iron supplementation.[102] Decreased reticulocyte Hgb is an indicator of the inadequacy of iron supply in the face of increased iron demand stimulated by ESA therapy.[103] The requirement for a kinetic balance between iron delivery and level of erythropoietin stimulation may explain the need for IV iron supplemental therapy in ESA-treated patients, even those with replete iron stores.[96] The clinical response to the combination of IV iron and ESA therapy may be attributed to the ability of the parenteral route to circumvent the inflammation-induced block to intestinal iron absorption and to deliver sufficient iron to the reticuloendothelial system, and the ability of ESA therapy to mobilize the iron from the reticuloendothelial system via transferrin into RBC precursors.[69,104,105] It is not clear how IV iron can enhance the effect of ESAs even in the face of apparently increased iron stores. It is possible that the additional iron load in the reticuloendothelial system increases iron efflux from macrophages, perhaps by increasing the translation of ferroportin mRNA.

Currently approved IV iron preparations are listed in Table 4.[69,106,107] The risk–benefit profile of IV iron continues to undergo evaluation in renal dialysis patients,[96,108] as well as in patients with anemia caused by other chronic diseases.[74] Iron dextran was the most widely used IV iron until the introduction of ferric gluconate, and then iron sucrose, to the U.S. market. Shortly thereafter, the use of iron dextran in dialysis patients decreased substantially because of the view that iron dextran carried a greater risk of severe reactions. Information in a retrospective analysis by Chertow et al.[109] of 50 million doses of IV iron found that low molecular weight (LMW) iron dextran was safer than high molecular weight iron dextran, with the latter agent accounting for the majority of reported serious adverse events attributed to iron dextran.

The clinical setting for which IV iron is to be used should determine which preparation is chosen. For total dose infusion, IV iron is required because the iron salts cause dose-dependent gastrointestinal or vasoactive reactions at doses > 200 mg to 400 mg.[110] The preferred dextran is the LMW preparation because as above, the high molecular weight preparation is associated with a significantly higher incidence of serious acute events.[109,111] For patients receiving cyclical therapies such as cancer chemotherapy or dialysis, the iron salts or LMW iron dextran can be used as 100-mg to 400-mg infusions.[93,110,112] In clinical settings such as preoperative

Table 4. Currently Available IV Iron Preparations

Trade name	DexFerrum	INFeD	Ferrlecit	Venofer	Feraheme	Ferinject[a]	Monofer[a]
Manufacturer	American Regent, Inc.	Pharmacosmos	Sanofi Aventis	Vifor	AMAG	Vifor	Pharmacosmos
Carbohydrate	High-molecular-weight dextran	Low molecular weight dextran	Gluconate	Sucrose	Carboxymethyl dextran	Carboxymaltose	Isomaltoside 1000
Molecular weight measured by manufacturer (Da)	265,000	165,000	289,000–440,000	34,000–60,000	750,000	150,000	150,000
Total-dose or >500-mg infusion	Yes	Yes	No	No	Yes	Yes	Yes
Premedication	TDI only	TDI only	No	No	No	No	No
Test does required	Yes	Yes	No	No	No	No	No
Iron concentration (mg/mL)	50	50	12.5	20	30	50	100
Vial volume (mL)	1–2	2	5	5	17	2 or 10	1, 2, 5 or 10
Black box warning	Yes	Yes	No	No	No	No	No
Preservative	None	None	Benzyl alcohol	None	None	None	None

Ferric gluconate and iron sucrose are also referred to as iron salts.
TDI = total-dose infusion.
[a]Not approved in the United States.
Adapted from Auerbach.[69]

patients, pregnancy, menometrorrhagia, gastric bypass, and uncomplicated iron deficiency in those intolerant to oral iron, however, a total dose infusion of LMW iron dextran is more convenient, equally effective, and less costly. Three studies comparing LMW iron dextran with the 2 salts show no difference in effectiveness or toxicity among the 3 products, but demonstrate considerable savings and increased convenience with LMW iron dextran.[113–115] Similar strategies can be used with the other available IV iron preparations (Table 4). For example, rapid, large, dose administration of ferric carboxymaltose was found to be more effective than oral iron therapy in correcting anemia and replenishing iron stores in women with dysfunctional uterine bleeding.[116]

IV iron can allow up to a 5-fold erythropoietic response to significant blood loss anemia in normal individuals.[117,118] A greater rate of RBC production is probably not possible unless red marrow expands into yellow marrow space, as is seen in patients with hereditary anemias.[119,120] One potential limitation to IV iron therapy may be that much of the administered iron ends up in the reticuloendothelial

Table 5. Currently Approved Prothrombin Complex Concentrate Products

	Factors levels (IU/mL)			
Product (manufacturer)	**II**	**VII**	**IX**	**X**
I. Available in the United States:				
A. PCCs, three-factor (II, IX, X)				
1. Profilnine SD (Grifols)[a]	≤150	≤35	≤100	≤100
2. Bebulin VH (Baxter)[a]	24–38	<5	24–38	24–38
II. Available outside the United States:				
A. PCCs, four-factor (II, VII, IX, X)				
1. Beriplex (CSL Behring)[b]	20–48	10–25	20–31	22–60
2. Octaplex (Octapharma)[c]	14–38	9–24	25	18–30
3. Cofact (Sanguin)[d]	14–35	7–20	25	14–35
4. Prothromplex T (Baxter)[e]	30	25	30	30
5. Proplex T (Baxter)[f]	20	20	20	20
B. PCCs, three-factor (II, IX, X)				
1. Prothromplex HT (Baxter)[g]	30	—	30	130
2. Prothrombinex VF f (CSL Bioplasma)	100	—	100	100
III. Activated PCC				
FEIBA (Baxter)[h]	32 ± 8	38 ± 5	35 ± 2.5	28 ± 5

The values given for factor contents are the number of units (IU/mL) present per 100 Factor IX units in each vial.
PCC = prothrombin complex concentrate.
[a]Product insert specifies: "Indicated for replacement of Factor IX in patients with hemophilia B. Not indicated for treatment of Factor VII deficiency."
[b]United Kingdom (UK), European Union (EU).
[c]UK, Canada, EU.
[d]EU.
[e]Austria.
[f]Japan.
[g]Australia.
[h]Factor VIII inhibitor bypass activity calculated for 25 U/mL vial. NB: product insert specifies that FEIBA is contraindicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to Factors VIII or IX.
Modified from Goodnough LT, Shander AS.[124]

Table 6. Published guidelines for acute reversal of warfarin coagulopathyin patients with intracerebral hemorrhage

Society (year)	Vitamin K	Plasma (mL/kg)		PCC (U/kg)	Reference
Australian (2004)	IV (5–10 mg)	Yes (NS)	AND	Yes (NS)[a]	(133)
EU Stroke (2006)	IV (5–10 mg)	Yes (10–40)	OR	Yes (10–50)	(134)
AHA (2010)	IV (NS)	Yes (10–15)	OR	Yes (NS)	(135)
French (2010)	Oral or IV (10 mg)	Yes (NS)[b]	OR	Preferred (25–50)	(136)
British Standards (2011)	IV (5 mg)	No		Yes (NS)	(137)
ACCP (2012)	IV (5–10 mg)	Yes		Preferred	(138)

PCC = prothrombin complex concentrate; rFVIIa; NS = not specified; ACCP = American College of Chest Physicians; EU = European Union; AHA = American Heart Association.

[a]If a 3-factor PCC is administered, fresh frozen plasma (FFP) is also recommended as a source of Factor VII.

[b]Use of plasma only when PCCs not available.

Updated from Goodnough LT, Shander AS.[124]

system as storage iron, from where it is not readily available for erythropoiesis,[120] particularly if hepcidin concentrations are elevated. For patients with absolute iron deficiency, 50% of IV iron is incorporated into Hgb within 3 to 4 weeks.[121] However, for patients with AI, IV iron is mobilized less rapidly from the reticuloendothelial system. Nevertheless, when iron dextran was given IV to patients with anemia of rheumatoid arthritis[122] and inflammatory bowel disease,[123] Hgb concentrations increased significantly.

HEMOSTATIC AGENTS

Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs), single-factor concentrates, and recombinant coagulation factors are approved and routinely used in the treatment of inherited coagulation factor deficiencies. Some of these products have also been approved as hemostatic agents in acquired coagulopathies, such as acute reversal of warfarin coagulopathy,[124] or may be considered (but are not approved) for acute reversal of oral Xa inhibitor therapy.[125] Currently approved PCCs are summarized in Table 5.

PCCs are either activated (i.e., to allow for bypassing inhibitors to Factor VIII or Factor IX in the treatment of patients with hemophilia A or B), or are nonactivated: some of these PCCs are approved for use in Factor IX deficiency (hemophilia B), of which some are approved for reversal of warfarin coagulopathy. The nonactivated PCCs are further categorized on the basis of the presence (4-factor) or absence (3-factor) of sufficient levels of Factor VII.[126] PCCs that contain all 4 (including Factor VII) of the vitamin K–dependent clotting factors are approved in the European Union (EU),[127] variably in other countries such as Canada and Australia, and are not yet approved in the United States. A 4-factor PCC product (Beriplex, CSL Behring, King of Prussia, PA)[128] is currently undergoing regulatory review in the United States for emergency reversal of warfarin coagulopathy in patients with major bleeding[128] and also for perioperative management of patients receiving warfarin therapy.[129] Three-factor PCCs are approved in the United States only for the replacement of Factor IX. Use of these 3-factor PCCs for reversal of warfarin is controversial; although they can be demonstrated to normalize International Normalized Ratio (INR),[130] one report showed a suboptimal effect in correcting INR because of minimal increments in levels of Factor VII.[126] In contrast, 4-factor PCCs are approved outside the United States for replacement of the vitamin K–dependent clotting factors (II, VII, IX, X).[131,132] A recent study demonstrated an effect of 4-factor PCC in acute reversal of rivaroxaban (Xa inhibitor) but not dabigatran (thrombin inhibitor) therapy in normal volunteers.[125]

Guidelines from a number of medical societies on the use of PCCs in these settings have been published. Five guidelines (Table 6)[133–138] have recommended that PCC can be given as an alternative to fresh frozen plasma (FFP) to increase levels of the vitamin K–dependent clotting factors. The most recently updated guidelines from the American College of Chest Physicians[138] recommend PCC therapy instead of plasma therapy for acute reversal of warfarin coagulopathy; however, currently, only 3-factor PCCs are approved in the United States. These have been demonstrated to be inferior to plasma therapy for acute warfarin reversal.[126] Accordingly, in one review, the authors have published their own hospital's trauma Coumadin protocol with a recommendation of concomitant administration of a 3-factor concentrate (4000 IU) and rVIIa (1.0 mg).[139] However, another review[140] concluded that PCC should be compared directly in randomized, controlled trials with other treatment strategies including FFP and rFVIIa, and should evaluate the effect on patient outcomes rather than simply the normalization of the INR, which has been used as a surrogate end point.[141] This lack of consensus on the role of PCC therapy relative to plasma therapy is in part attributed to the variability in the contents and levels of clotting factors in these preparations;[126,142] their regulatory approval status for different countries; their lack of availability among hospital formularies, particularly in smaller community hospitals; and their potential risks of thrombogenicity.

Product information for activated PCCs such as Factor VIII inhibitor bypass activity (FEIBA VH Immuno, Baxter, Vienna, Austria) and Autoplex-T (Baxter, Roundtree, IL) state, under warnings, that they "must be used only for patients with circulating inhibitors to one or more coagulation factors and should not be used for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to Factors VIII or IX."[143,144] In addition, the presence of disseminated intravascular coagulation is a stated contraindication to their use in the package inserts. Nevertheless, despite the even greater potential risk of thrombogenicity compared with nonactivated PCCs, use of FEIBA has been recommended for reversal of warfarin in life-threatening bleeding if 4-factor PCCs are not available.[145] A chart review of 72 patients who received FEIBA for warfarin reversal compared with 69 patients who were

treated with FFP in life-threatening bleeding, indicated faster and more effective reduction of INR with FEIBA, but similar survival rates and length of hospital stay between the cohorts. However, 7% of the FEIBA-treated patients suffered potentially related adverse events.[145]

The safety of PCC concentrates in the setting of emergency reversal of warfarin coagulopathy remains a subject of debate. A recent prospective study of 173 patients treated with PCC found that 4.6% of patients had a thrombotic event, but it attributed these adverse events to cessation of anticoagulant therapy for underlying and continuing risks of thrombosis.[146] A recent study in a pig model of coagulopathy with blunt liver injury found that whereas 35 IU/kg PCC improved coagulation and attenuated blood loss, increased doses (50 IU/kg) of PCC therapy seemed to increase the risk of thromboembolism and disseminated intravascular coagulation.[147] Thrombogenicity has been a recognized problem for patients,[148,149] in part related to the presence of activated clotting factors (for which heparin and antithrombin III have been added to some preparations[150]); and also in part because of the presence of other preexisting thromboembolic risk factors that resulted in initiation of warfarin in these patients (e.g., venous thrombosis, atrial fibrillation) or new, concurrent risk factors (e.g., trauma, head injury).

The reported incidence of thromboembolic events published between 1998 and 2008 ranged from 0% to 7% (overall weighted mean of 2.3%), with higher and repeated dosing potentially associated with higher risk.[140] Multinational trials on patients receiving a 4-factor PCC product at various infusion speeds for urgent vitamin K antagonists reversal have supported the safety and effectiveness of rapid infusion of PCC in these patients.[151,152] However, noteworthy for one recommendation is "whenever possible, patients receiving PCCs should be under low dose heparin prophylaxis,"[142] underscoring that use of PCCs in this setting is accompanied by risks of thrombosis. A recent review[153] of 8 clinical studies identified a thromboembolic event rate of 0.9% associated with PCC therapy. Studies of optimal dosing strategies for PCC, including fixed versus variable (weight-based) dosage, provide a basis for future research.[154]

As pooled blood product derivatives, PCCs also have potential risks of transmitting infectious agents.[155] Various processing methods such as nanofiltration, solvent detergent treatment, or vapor heating have been used to inactivate pathogens in commercially available PCCs and pooled plasma products.[156] The cost-effectiveness of such products with pathogen reduction technology is an area of current debate.[157,158]

Antifibrinolytics

Reducing and/or avoiding blood loss is a key component of patient blood management.[2] Under physiologic conditions, hemostasis is achieved through constriction of damaged vessels, formation of platelet plug, and activation of coagulation factors resulting in the formation of a stabilized fibrin clot at the site of bleeding. Parallel to this, the fibrinolytic system is activated to control clot formation and propagation and dissolve the unnecessary (and potentially dangerous) clots.[159,160] Hemostatic agents exploit these physiologic pathways to tip the balance toward forming and maintaining clots, thereby reducing bleeding.[160,161]

The most widely studied and used hemostatic agents are the antifibrinolytics. As the name implies, these agents act by inhibiting the physiologic fibrinolytic pathway that is responsible for limiting and dissolving clots. Aprotinin is a serine protease inhibitor that directly inhibits plasmin (and many other serine proteases), whereas lysine analogous, ε-aminocaproic acid (EACA), and tranexamic acid (TXA), act through interfering with the activation of plasminogen to plasmin and its binding to fibrin clots.[162] In addition, aprotinin inhibits the contact activation pathway and may attenuate the inflammatory response in cardiopulmonary bypass (CPB).[163] Aprotinin was removed from the market in 2007, but a reexamination of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study[164] and other data have led to a reversal of this decision and reintroduction of aprotinin in Canada and Europe for cardiac surgery. TXA and EACA have also been extensively reported in clinical investigations on antifibrinolytics in various patient populations.[165]

Renewed interest in antifibrinolytics, especially TXA, comes from the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial in which more than 20,000 bleeding (or at risk of bleeding) trauma patients were randomized to receive TXA versus placebo. It was noted that despite no difference in bleeding and transfusions, early treatment with TXA compared with placebo was associated with a risk of death of 14.5% vs 16%, respectively.[166] Nevertheless, acceptance of the CRASH-2 study results remains slow in the United States despite widespread implementation of TXA into clinical practice in Europe.

Further studies have analyzed bleeding and transfusions in other settings. Crescenti et al.[167] randomized 200 patients undergoing radical retropubic prostatectomy to TXA versus placebo and observed a perioperative transfusion rate of 34% vs 55% in the study arms, respectively, with no increased risk of thromboembolic events. Zufferey et al.[168] studied 110 patients undergoing surgery for hip fracture and reported a significantly lower RBC transfusion rate in patients randomized to TXA versus the placebo arm; however, the rate of occurrence of vascular events in the 6-week postoperative period was 16% in the TXA arm versus 6% in the placebo arm. This observation did not reach statistical significance, underscoring the need for further studies with larger sample sizes. Another study evaluating 900 prospective controlled cases of combat injuries found that TXA was independently associated with survival (odds ratio, 7.23), with a lower unadjusted mortality rate (17.4%) compared with the no-TXA group ($P = 0.03$). The authors called for inclusion of TXA in trauma protocols.[169] Many European and Canadian massive transfusion protocols include TXA as part of their management. Investigation through a large randomized trial[170] of postpartum hemorrhage, still the number one cause of mortality in the parturient, is in progress.

A systemic review of trials in off-pump coronary artery bypass graft (CABG) surgery concluded that TXA administration (1–2 g loading dose and 200–400 mg/h) was associated with significantly less risk of transfusion with no increased risk of complications.[171] Another meta-analysis of

252 randomized, controlled trials (including the CRASH-2 study) has concluded that aprotinin was marginally superior to lysine analogs with regard to reducing blood loss. Compared with placebo, RBC transfusion was reduced by 34%, 39%, and 19% in patients treated with aprotinin, TXA, and EACA, respectively. Contrary to the other recent reports, aprotinin was not found to be associated with increased risk of mortality, myocardial infarction, stroke, or renal dysfunction in the meta-analysis when compared against placebo, although the authors raised issues with the adequacy of the data. On the other hand, lysine analogs were associated with decreased risk of mortality compared with aprotinin, a finding heavily influenced by the data from the BART study.[172]

Another meta-analysis focusing primarily on the safety of TXA confirmed less mortality in patients treated with TXA compared with no treatment, but also indicated a non-significant trend toward increased neurologic complications including seizures.[173] Overall, the available data support the safety and effectiveness of lysine analogs for reducing blood loss and improving the outcomes of the patients. Again, it should be noted that Health Canada has recently reversed its decision on suspending aprotinin from the market, and has allowed its use as a hemostatic agent to reduce surgical blood loss in patients undergoing low-risk CABG procedures, while placing a boxed warning on the product labeling and requesting the manufacturer to conduct additional safety and effectiveness studies.[174] Similarly, on the basis of a new review of data from the BART study and other evidence and by noting a number of problems with the BART study, the European Medicines Agency recently recommended that the suspension of aprotinin for patients undergoing cardiac bypass surgery be lifted.[175]

Desmopressin

Desmopressin (a long-acting vasopressin agonist) is indicated to maintain hemostasis in patients with hemophilia A or mild to moderate type-1 von Willebrand disease with Factor VIII activity >5%.[176] Although desmopressin contributes to hemostasis through increasing the levels of von Willebrand factor and Factor VIII and improving platelet function among other less understood mechanisms, its effects are far more diverse and include inducing the production of nitric oxide (resulting in vasodilation) and increasing the level of tissue plasminogen activator.[177] Desmopressin has been used as a hemostatic agent in patients without preexisting coagulation disorders undergoing high blood loss surgeries such as cardiac, spinal, and orthopedic procedures. A meta-analysis of 38 randomized, placebo-controlled trials indicated that desmopressin (usually at a dose of 0.03 μg/kg) had a statistically significant (albeit clinically modest) effect on reducing perioperative bleeding and transfusion of blood components (reducing approximately 80 mL in blood loss and 0.3 units in transfusions).[178] There was no significant increased risk of thromboembolic complications,[178] a concern that had been reported in earlier studies.[179] Some reports suggest that patients with platelet dysfunction (e.g., due to aspirin) are more likely to benefit from desmopressin although more data are needed.[179] However, its routine use as a prophylactic hemostatic agent is still debated and not currently recommended in cardiac surgeries.[180]

Other Factor Concentrates

Various concentrated or recombinant coagulation factors are available and routinely used in the treatment of congenital deficiencies; some of these factors have also been considered and investigated as potential hemostatic agents. Fibrinogen concentrate is currently approved in the United States for treatment of bleeding in patients with congenital fibrinogen deficiency.[181] However, given the assertion that acquired fibrinogen deficiency may be present in patients undergoing various high blood loss procedures, use of fibrinogen concentrate as a hemostatic agent is under investigation. In a pilot study, thromboelastometry-guided administration of fibrinogen concentrate to patients undergoing aortic valve operation and ascending aorta replacement to achieve a high-normal plasma level resulted in less blood loss and transfusions.[182] Another study by this team reported that administration of fibrinogen concentrate in patients with decreased platelet function with bleeding after CABG surgery was associated with less transfusion of allogeneic blood components.[183] Encouraging reports have been published on the use of fibrinogen concentrate as a hemostatic agent in bleeding trauma patients, but the evidence is still far from conclusive in these and other patient populations.[184–186] Finally, fibrinogen concentrates have been reported to be an effective addition to conventional treatments for obstetrical hemorrhage associated with hypofibrinogenemia.[187,188] Fibrinogen concentrates are used in certain countries where cryoprecipitate is not available.

Factor XIII concentrate and recombinant forms are available for clinical use in Europe, but still await regulatory approval in the United States. Factor XIII is primarily used for prophylactic treatment of patients with congenital deficiency of Factor XIII. However, its special mode of action through cross-linking fibrin and improving the clot firmness may be a promising process to exploit for hemostasis, particularly in procedures associated with extensive perioperative blood loss. In a preliminary study in patients undergoing CABG with CPB, administration of Factor XIII was suggested to be effective in reducing postoperative blood loss and transfusions, only in patients with lower than normal Factor XIII.[189] More recently, a placebo-controlled, proof-of-concept, randomized trial in 22 patients undergoing elective gastrointestinal cancer surgery has indicated that early administration of Factor XIII during surgery may be able to promote fibrin clot firmness and reduce fibrinogen consumption and blood loss.[190] The blood conservation guidelines from the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists have recommended Factor XIII as a hemostatic agent to stabilize the clots in bleeding patients undergoing cardiac surgery when other treatments have not yielded satisfactory results.[180] A Phase-II, multinational, randomized, placebo-controlled trial on the safety and effectiveness of recombinant Factor XIII in reducing transfusions in 479 patients undergoing heart surgery with CPB did not indicate any effectiveness.[191] At this point, it seems that more data are needed to support its routine use as a hemostatic agent.

Topical Hemostatic Agents

Topical application of hemostatic agents provides a way of maximizing the local effects of these agents while minimizing

their (potentially unwanted) systemic effects. Although there are a multitude of publications demonstrating bleeding cessation with a variety of topical agents, few if any address the use of topical agents, other than the antifibrinolytics, as a direct effect on transfusion reduction. In one systematic review,[192] the authors report the effectiveness of topical agents in transfusion reduction and point out the paucity of strong trials in this area. As part of a multimodal approach to blood conservation in cardiac surgery, topical agents have been and continue to be recommended.[180] In a placebo-controlled, randomized trial of 124 total knee arthroplasty patients (with a high patient dropout rate of 20%), topical application of TXA (1.5 g or 3.0 g of TXA in 100 mL normal saline solution applied topically to the joint for 5 minutes at the end of surgery) reduced postoperative blood loss by 20% to 25% depending on the dose, without any reported side effects.[193] A meta-analysis of 8 trials on 622 on-pump cardiac surgery patients concluded that topical application of aprotinin or TXA to the mediastinum or pericardial cavity was associated with an average of 220 mL reduction in 24-hour postoperative blood loss via chest tube and avoidance of transfusion of 1 unit of RBC per patient with no reported adverse effects.[194] It is interesting to note that one of the analyzed trials compared topical versus systemic aprotinin and found similar results.[195]

Several other topical products are available in the form of tissue sealants and adhesives for clinical use today. Topical hemostats generally act by compressing the bleeding vessels (directly or indirectly as a result of swelling of the sealant and compression of the adjacent tissues), activating/aggregating platelets, and providing a physical scaffold for better clot formation. In addition, some incorporate various procoagulant factors for more effective hemostasis. The matrix of these products is commonly made of collagen, gelatin, or polysaccharides (e.g., cellulose, chitin). Some other topical agents are made of synthetic or semisynthetic compounds such as cyanoacrylate, polyethylene glycol, and a mixture of albumin and glutaraldehyde that are polymerized to form tissue adhesives.[196–198] Thrombin and fibrinogen are increasingly used as part of topical sealants (or on their own such as topical thrombin spray) to enhance the hemostatic effects of these products.[199–201]

Several randomized, controlled trials have demonstrated the safety and effectiveness of tissue sealants and adhesives, although negative results have also been reported. For example, in a study of 415 patients undergoing elective cardiac and aortic procedures, use of a thrombin-containing gelatin-based sealant was associated with better and faster hemostasis and less postoperative bleeding and transfusions.[202] Similarly, use of fibrin sealants (potent topical hemostatic products containing both thrombin and fibrinogen) was found to reduce perioperative blood loss by more than 20% in 81 patients undergoing total hip replacement.[193] On the other hand, a randomized, controlled trial of 300 patients undergoing liver resection failed to show any difference between fibrin sealant and placebo with regard to transfusion, postoperative and total drainage, complications, and postoperative morbidity,[203] although the coupled use of an argon beam coagulator or a bipolar surgical sealer in all patients might have contributed to lack of significant differences between the study arms.[204]

However, trials evaluating the topical hemostatic agents are relatively small, and recent meta-analyses pooling data from several studies focusing on their effect on blood loss or transfusions are largely lacking. A 2003 meta-analysis of 7 trials on the effects of fibrin sealants on perioperative transfusion concluded that these products reduced allogeneic RBC transfusions by 54%, but it also noted the limited sample size and lack of blinding as causes for concern on methodological robustness of the studies.[205] A 2009 update of this meta-analysis evaluated data from 18 trials and concluded that fibrin sealants reduced allogeneic RBC transfusions by 37% and reduced blood loss by an average of 161 mL per patient. The effect was even larger in a subset of trials focusing on orthopedic surgeries. Despite more convincing data, the call for larger and better- designed trials remains.[206]

The topical hemostatics are generally safe and the complications are mostly limited to issues related to local compression (for products that swell after application) and residual risk of disease transmission (for products derived from human or animal sources).[198] The fibrin sealant meta-analysis could not find an association between use of fibrin sealants and increased risk of infections, hematoma formation, or death.[206] Induction of inhibitory antibodies is also a concern, particularly in the case of bovine thrombin with potential cross-reactivity against the human native protein, which could result in coagulopathy and bleeding. This complication resulted in issuing a black box warning on the package insert of topical bovine thrombin. The risk appears to be vastly eliminated when recombinant human proteins are used.[207,208] A study of data from 8 clinical trials on topical recombinant thrombin (used as part of sealants or directly applied) has concluded that recombinant thrombin was well tolerated. New thrombin antibodies emerged in less than 1% of the patients, and these antibodies were not neutralizing and hence not expected to negatively affect coagulation.[209]

Local infiltration of vasoconstrictors such as epinephrine has been used in clinical practice for years to reduce bleeding, namely in skin incisions and oral/dental surgeries.[210] These topical hemostatic agents can be highly effective,[211] but they must be used carefully to avoid systemic reactions, particularly in patients with cardiovascular comorbidities.[212–214]

Recombinant Activated Factor VII

rFVIIa is thought to act via 2 mechanisms, both of which are to increase coagulation activation to the site of tissue damage.[215] First, rFVIIa complexes directly with tissue factor (TF) released from the subendothelium at sites of vascular disruption. The TF-rFVIIa complex then activates the remainder of the common coagulation cascade via activated Factor X. Alternatively, rFVIIa may bind to activated platelets, which also concentrates Factor X activation to sites of tissue injury. The Factor Xa generated by these 2 mechanisms ultimately drives the thrombin burst, which cleaves fibrinogen to fibrin, thus initiating the formation of the fibrin meshwork critical to secondary coagulation and clot stabilization. The potential role for rFVIIa in TF-independent clotting has raised concern for its site specificity and the risk for off-target thrombosis. Accordingly, the FDA required the addition of a black box warning to the package insert in 2005, warning physicians of the risk of thromboembolic complications when the agent

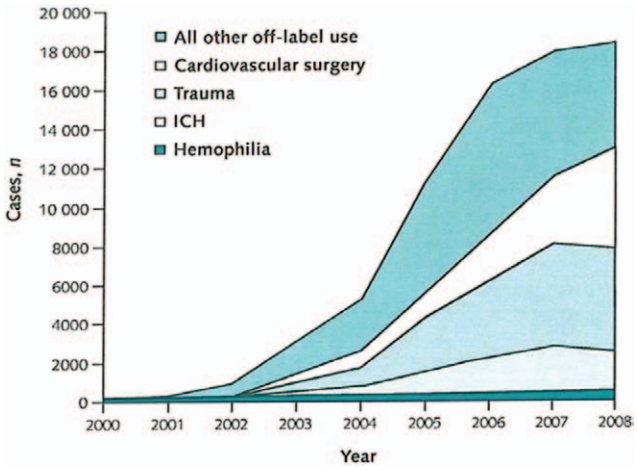

Figure 2. Estimated annual in-hospital cases of recombinant Factor VIIa use for hemophilia and off-label indications. Cases signify the number of hospitalizations during which recombinant Factor VIIa was used. All cases for each year are depicted. The width of each segment represents the number of cases for each category, as indicated by differential shading. Hemophilia includes hemophilia A and B, and trauma includes body and brain trauma. ICH = intracranial hemorrhage. Adapted from Logan AC et al.[216]

is used, in view of these safety concerns for thromboembolic adverse events, along with continued uncertainty regarding its level of effectiveness in off-label settings.

Approved indications of rFVIIa in the United States and EU include treatment of bleeding episodes (or prevention of bleeding from invasive procedures) in patients with congenital hemophilia A or B with inhibitors to Factors VIII or IX, patients with congenital Factor VII deficiency, and in patients with acquired hemophilia. In addition, it is approved in the EU in the treatment of Glanzmann thrombasthenia for patients with an inherited qualitative platelet defect . However, these approved indications accounted for only 3121 (4.2%) of 73,747 cases reported to use rFVIIa in the United States from 2000 to 2008.[216]

Off-label use of rFVIIa in a variety of other clinical settings has continued to increase rapidly (Fig. 2). For example, use of rFVIIa in patients not receiving warfarin who had spontaneous intracranial hemorrhage (ICH) increased 8-fold, from 250 cases in 2004 to 2010 cases in 2008, accounting for 11% of all off-label rFVIIa usage. This activity reflected a large dose-seeking clinical trial in patients with spontaneous ICH that initially showed promise[217] in reducing the volume of hemorrhage and improved patient outcomes (reduced mortality, long-term disability); however, the subsequent trial,[218] although it confirmed reduced hematoma growth, was unable to demonstrate improved patient outcomes (reduction of severe disability or death at 90 days).

Other off-label categories include cardiovascular surgery and trauma in an attempt to address uncontrolled hemorrhage in these settings. Gill et al.[219] reported significant reductions in bleeding, transfusion requirements, and reexploration when rFVIIa was used postoperatively in high-risk bleeding cardiac surgical patients. Finally, early reports of the off-label use of rFVIIa in the successful management of warfarin-associated ICH in patients with refractory bleeding led to the development of policies for oversight of its off-label use.[220] A subsequent systematic literature review found only limited available evidence for 5 off-label clinical settings (Fig. 2), in which no mortality reduction was found to be associated with rFVIIa use in these settings.[221]

The potential role of rFVIIa therapy in patients taking oral thrombin or Xa inhibitors who have hemorrhagic complications remains undefined. A recent case report suggested that the combination of rFVIIa and hemodialysis was effective in management of dabigatran-associated bleeding in a patient after cardiac surgery[222] but the patient also received multimodal therapy.

Case reports have described the successful use of rFVIIa in patients with warfarin-associated anticoagulation and ICH,[223–225] and studies have indicated that doses of 15 μg/kg to 20 μg/kg rFVIIa can normalize INR values when used to treat warfarin-associated deficiencies of functional vitamin K–dependent clotting factors.[226] Nonetheless, concerns have been raised whether the effect goes beyond mere normalization of INR, and whether patient outcomes are improved.[227] The uncertainty on whether the demonstrable effects of rFVIIa on INR correction are accompanied by adequate restoration of thrombin generation[228] compared with PCCs, or improvement in bleeding times in reversal of warfarin in normal subjects,[229] are reasons why 2 guidelines[135,137] and 1 evidence-based review[227] have recommended against the routine use of rFVIIa for warfarin reversal in patients with ICH.[135]

The safety profile of rFVIIa in controlled trials in patients with spontaneous ICH suggests that an increased risk of thrombotic arterial events may be underreported by treating physicians.[230] Thromboembolic events associated with rFVIIa were reported to the FDA in approximately 2% of treated patients in clinical trials, but sufficient data were not available to identify the incidence in patients who received rFVIIA for warfarin reversal.[231] A review of 285 trauma patients revealed that 27 (9.4%) had thromboembolic complications after administration of rFVIIa, including 3 patients who were treated for warfarin reversal.[232] Levi et al.[233] recently analyzed 35 randomized trials of rFVIIa with 4468 subjects and found that 11.1% had thromboembolic events. Rates of venous thromboembolic events were similar for subjects who received rFVIIa compared with placebo (5.3% and 5.7%, respectively); arterial events, however, were significantly higher (5.5% vs 3.2%, $P < 0.003$) in subjects receiving rFVIIa compared with placebo, particularly for older patients and/or higher doses.

Artificial Oxygen Carriers

Total oxygen carried by the blood is the sum of oxygen carried by Hgb molecules (normally confined within RBCs) and the oxygen dissolved in the plasma. The former component is determined by the Hgb concentration in blood and the percentage of Hgb oxygen saturation, whereas the latter component is directly related to the partial pressure of oxygen in the blood.[234,235] Under physiologic conditions, each gram of Hgb is capable of binding approximately 1.34 mL oxygen, whereas each mL of plasma is capable of dissolving approximately 0.03 mL oxygen at 37°C and arterial partial pressure of oxygen in the blood of 100 mm Hg.[234,236] Hence, most of the oxygen molecules (approximately 98%) are transported in blood via the first mechanism.[236] Both mechanisms have been used as means for urgent increasing

of the oxygen delivery in cases of severe anemia when blood oxygen content cannot meet the tissue demands and when blood transfusion is not an option. For example, in hyperbaric oxygen therapy, oxygen at above atmospheric pressure is administered to increase the amount of oxygen dissolved in plasma and causes a boost in tissue oxygen delivery that may indeed be enough to save a severely anemic patient from imminent death or ischemic complications.[237] On the other hand, products known as artificial oxygen carriers achieve this by supplying additional Hgb molecules (first mechanism), or by providing an inert medium capable of dissolving substantial amounts of oxygen (second mechanism).

Although no artificial oxygen carrier is currently approved by the FDA for clinical human use in the United States, this is a field of active research with several products in various stages of development. The future of artificial oxygen carriers seems promising, given several potential advantages of such products. Some aspects that make the artificial oxygen carriers particularly appealing include: prospect of being free of most or all of the infectious risks of allogeneic blood; no need to perform blood grouping and cross-match; extended shelf-life and possibility of storage at room temperature; potential for virtually unlimited supply; and possibility of development of homogenous and standardized products with controlled characteristics optimized to achieve the goal of oxygen delivery without raising all other complexities of allogeneic blood that have been rightfully likened to a tissue transplant.[1,236,238,239]

Perfluorocarbon (PFC) emulsions are the most studied products that can boost oxygen delivery by increasing the amount of dissolved oxygen. To maximize their effectiveness, use of these oxygen carriers must be coupled with oxygen and increased F_{IO_2} to further increase the amount of dissolved oxygen. Although PFCs are biologically inert, the same does not necessarily apply to other chemicals present in these products (e.g., surfactants added for emulsification). The PFCs that have reached clinical trial include Fluosol-DA (Alpha Therapeutics, Los Angeles, CA) and Oxygent (Alliance Pharmaceutical Corporation, San Diego, CA; and Perftoran [OJCS SPF Perftoran Russian, Moscow, Russia] outside of the United States).[240] Fluosol-DA was initially used to improve oxygen delivery to the heart muscle during percutaneous transluminal coronary angiography, but it was subsequently withdrawn because of difficulties in storage and preparation, and lack of need in angioplasty. Oxygent has been shown in numerous studies to be able to improve oxygen delivery and replace and reduce transfusions, with overall mild side effects with the exception of a reported increase in stroke.[236] Transient thrombocytopenia is a common side effect of PFCs, possibly related to increased platelet destruction because of changes in platelet membrane in presence of PFCs.[241]

On the other hand, Hgb-based oxygen carriers (HBOCs) dramatically increase oxygen delivery through increasing the Hgb level. The Hgb may be from human, animal, or recombinant sources. Despite effective oxygen transportation, HBOCs have been associated with complications such as vasoconstriction (initially attributed to extravasation of the HBOC to interstitial space and scavenging nitric oxide),[242] hypertension, and renal, pancreatic, and liver injury. To minimize toxicity and associated complications, approaches such as purification, polymerization, cross-linking, conjugating with other macromolecules, and encapsulating in vesicles or other nano-particles have been pursued in various generations of HBOCs.[243]

Three products, HemAssist (Baxter, Deerfield, IL), Hemopure (Biopure, Cambridge, MA; now, OPK Biotech, Cambridge, MA), and PolyHeme (Northfield, Evanston, IL) are among the most extensively clinically investigated HBOCs. HemAssist (also known as diaspirin cross-linked Hgb or DCLHb) was produced from outdated human allogeneic blood units and had an Hgb concentration of 10 g/dL.[244] The product underwent relatively extensive animal and human studies, including a U.S. multicenter, randomized trial on 112 patients with traumatic hemorrhagic shock using normal saline as the control treatment, which indicated a 72% higher mortality rate in the DCLHb group and resulted in premature termination of the study.[244,245] Another prematurely terminated multicenter trial in Europe on 121 trauma patients with severe hemorrhagic shock concluded that treatment with DCLHb (versus standard therapy) reduced the use of transfusions, without improving morbidity or mortality.[246] Two follow-up studies by the investigators reanalyzed the data from these 2 trials, and concluded that for the most part, DCLHb use was not associated with arterial blood pressure variation, base deficit, or lactate abnormalities (indicative of poor perfusion), and as such, they concluded that increased mortality in the DCLHb arm is not directly related to the vasoconstrictive effect of the product.[245,247] The manufacturer has suspended the development of HemAssist.

Hemopure (also known as HBOC-201) is polymerized, purified bovine Hgb with an Hgb concentration of approximately 13 g/dL and extended shelf-life. A Phase-III, randomized trial on 688 orthopedic surgery patients with RBC transfusion as the comparator reported that HBOC-201 was highly effective in eliminating the need for transfusions, but it was also associated with increased risk of adverse events (namely, increased systolic and diastolic blood pressure) and serious adverse events (cardiac events and strokes). The authors attributed the increased risk of unfavorable outcomes partially to imbalances in patients' age, intravascular volume overload, and undertreatment with the product.[248] Further randomized trials on HBOC-201 were abandoned in the United States out of concerns with the product's safety. However, the FDA provided a per-patient approval to use HBOC-201 on compassionate basis in patients with life-threatening anemia who could not have been transfused, and a report of 54 such cases has suggested that earlier administration of HBOC-201 to patients likely to have Hgb concentrations below critical levels is associated with better survival.[249] HBOC-201 became the first product in this class to be approved for human use in South Africa (2001) and Russia (2011) for treatment of acute anemia. However, the product's website in South Africa lists it as "unavailable" as of November 2011 (http://www.hemopure.co.za). A related product, HBOC-301 (Oxyglobin) is the first product approved in the United States and the EU for veterinary use, with promising results from ongoing investigations.[250–252]

PolyHeme is based on cross-linked and polymerized human Hgb sourced from outdated allogeneic RBC units, with an Hgb concentration of 10 g/dL.[244] In a Phase-III, multicenter trial in the United States, 714 trauma patients with hemorrhagic shock were randomized to field resuscitation with PolyHeme or crystalloid and reported lower use of allogeneic blood transfusions but a moderately higher risk of adverse events and serious adverse events (notably, myocardial infarction) in patients randomized to receive PolyHeme. However, the authors concluded PolyHeme had a favorable benefit-to-risk ratio in patients in need of transfusion when blood transfusion was not available.[253] A post hoc analysis of the data by the investigators suggested that PolyHeme was able to sustain postinjury survival longer compared with the control treatment.[254] It should be pointed out that the design of this trial, including the waiver of informed consent, the potential for increased adverse events, and the continued use of the compound when blood was available, has generated ethical controversies.[255–257] The manufacturer of PolyHeme eventually filed for bankruptcy.

Despite effectiveness in reducing allogeneic transfusions, clinical use of all major HBOCs appears to be marred with increased risk of morbidity and mortality. A 2008 meta-analysis of 16 trials on 5 different HBOCs (including the 3 products discussed here) indicated that regardless of the individual product or indication studied, use of these HBOCs was associated with significantly higher risk of death (relative risk of 1.30) and myocardial infarction (relative risk of 2.71) combined with the controls.[258] Although the methodology of this meta-analysis and the validity of the conclusions have been criticized, there is little doubt regarding the risks and complications of these products.[259,260] Nonetheless, there are also reports of patients with exceedingly low Hgb (even 2–3 g/dL) who survived on HBOCs.[249,259,261] The brief overview of these once promising artificial oxygen carriers summarizes the complexities faced by research and development efforts in this field. Although a new generation of products is in development, currently these products can be considered to help patients survive critically low Hgb levels when blood transfusions are not available, as "oxygen bridges" until compensatory erythropoiesis can be achieved with the use of such agents as ESA and IV iron therapies.

Intravascular volume expanders can also serve as pharmacologic alternatives to blood transfusion. Hemospan is a polyethylene glycol-modified human Hgb with improved half-life in blood circulation and relatively high affinity for oxygen, which may make it more effective in delivering oxygen to hypoxic and ischemic tissues. In 2 related randomized trials in a total of 841 patients undergoing hip arthroplasty, Hemospan use was shown to be more effective in preventing hypotensive episodes and reducing the duration of such episodes, compared with hydroxyethyl starch. While serious adverse events occurred similarly in both study arms, the incidence of nonserious adverse events such as nausea, oliguria, and hypertension was higher in patients randomized to receive Hemospan hydroxyethyl starch.[262,263] Currently, a Phase-II, randomized, controlled trial to evaluate the safety and effectiveness of Hemospan in trauma patients with shock is underway outside the United States.

CONCLUSION

Health care faces new challenges in delivery of care and resource utilization. The change from "volume-based" to "values-based" care necessitates shared decision making between patient and clinicians to achieve the best outcome.[264,265] In light of this, we have presented a review of the pharmacologic and hemostatic agents that are used in patient blood management with an emphasis on their clinical utility as alternatives to allogeneic blood transfusion. Both patients and physicians will require effective information to make the most appropriate health decisions in the context of informed consent.[266] As patient blood management evolves, understanding the relative benefits and risks of pharmacologic alternatives to blood compared with the relative benefits and risks of blood transfusion becomes imperative.

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