Prevention and Management of Hospital-Acquired Anemia

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KEYWORDS

• Hospital-acquired anemia • Iron deficiency anemia • Transfusion

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Anemia can be categorized as severe (hemoglobin [Hgb] level <9 g/dL), moderate (Hgb 9.1–11.0 g/dL), and mild (Hgb >11.0 g/dL).
2. Hospital-acquired anemia (HAA) is prevalent in the intensive care unit as well as on the wards.
3. Every patient who is admitted to the hospital is at risk of developing HAA. Those who are anemic before admission are at risk of worsening anemia during hospitalization.
4. Causes of HAA include blood draws, erythropoietin (EPO) (Amgen Inc, Thousand Oaks, CA, USA) suppression caused by increase in inflammatory markers from acute illness, and downregulation of iron.
5. HAA recognition and treatment affect patient outcomes.
6. Prevention and management of HAA demand a team approach and a culture that supports recognition and reduction of unnecessary laboratory testing and procedures.
7. Pharmacologic treatment continues to evolve, and evidence-based use of intravenous iron and EPO may have a role in supporting erythropoiesis to help prevent transfusion.

INTRODUCTION

It is an exciting time to be in health care, but there are many challenges. National attention to health care reform has reinforced the push for quality and value. The increasing cost of health care has health systems reassessing their efficiency and current business models. However, our population continues to age, with ever-growing comorbidities that require chronic medical care.

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The Affordable Care Act is expected to increase hospital admissions once it is in full effect, as the number of insured individuals increases. This demand for health care must be met not only with a supply of physicians to provide medical treatment but a health system capable of delivering high-quality medical care. Hospital-acquired anemia (HAA) was first recognized in the late 1970s as a consequence of the numerous tests and procedures that patients endure during their stay. Almost 4 decades later, we still struggle to recognize and manage the detrimental effects of HAA in our patients. It is the aim of this review to discuss and understand the importance of recognizing HAA and effectively compose a treatment plan to improve patient outcomes.

DEFINITIONS

1. What is the definition of anemia?

Anemia is defined as a reduction in 1 or more of the major red blood cell (RBC) measurements, which are obtained by a serum complete blood cell count: hemoglobin (Hgb) concentration, hematocrit, or RBC count. There has been some debate in defining the normal range. The World Health Organization (WHO) defines the criteria for men as Hgb levels less than 13 g/dL, and for women, less than 12 g/dL.[1] Various other investigators have proposed different lower limits, as shown in **Table 1**.

It is apparent when looking at these levels that there is debate regarding which parameters define the normal range. Several variables may affect baseline Hgb concentration, such as volume status, altitude of residence, level of physical activity, ethnicity, and advanced age. So, the first challenge becomes how to define anemia.

The WHO standard is widely used in epidemiologic studies, but is now more than 4 decades old. Beutler and Waalen[3] argued that the WHO criteria were mere approximations. Moreover, current laboratory testing eliminates many of the potential limitations of previous methodologies, thus making current laboratory testing more accurate. These investigators compared the 2 largest databases: NHANES III (the third US National Health and Nutrition Examination Survey) and the Scripps-Kaiser database, which collected data in San Diego between 1998 and 2002. Thus, in most recent research studies, anemia is defined using these criteria, highlighted in **Table 1**, which take under consideration age, sex, and ethnicity.

Table 1
Various lower limits of Hgb level in defining anemia

	Men (g/dL)	Women (g/dL)
Revised WHO/National Cancer Institute[2]	<13	<12
NHANES (National Health and Nutrition Examination Survey) III and Scripps-Kaiser studies[3]	White men Age 20–59 y <13.7 Age ≥60 y <13.2 Black men Age 20–59 y <12.9 Age ≥60 y <12.7	White women Age 20–59 y <12.2 Age ≥50 y <12.2 Black women Age 20–59 y <11.5 Age ≥50 y <11.5
Beutler et al,[3] 2006	13–14.2	11.6–12.3
Jandi,[4] 1996	14.2	12.2
Lee et al,[5] 1998	13.2	11.7
Tietz,[6] 1995	13.2	11.7
Hoffman et al,[7] 2004	13.5	12.0

2. What is the definition of HAA?

HAA is defined as anemia that develops during hospitalization in patients who have a normal admission Hgb level.[8] Anemia can be further categorized as severe (Hgb level <9 g/dL), moderate (Hgb level 9.1–11.0 g/dL), and mild (Hgb level >11.0 g/dL).[8]

EPIDEMIOLOGY

1. What is the prevalence of HAA?

It would be advantageous to have a national database for the prevalence of HAA. Although studies have been performed around the world, no study has consolidated the data to report a single percentage summarizing the prevalence of HAA. Throughout the world, there seems to be a consensus that HAA is common and that its prevalence may have implications on patient outcomes before and after discharge. On general internal medicine wards, a study by Thavendiranathan and colleagues[9] suggested that the mean change in Hgb level from admission to discharge was 7.9 g/L, with a corresponding mean change in hematocrit level of 2.1%. As early as 1973, Drs Elaine Eyster and James Bernene reported in the *Journal of the American Medical Association* that after measuring Hgb and hematocrit levels in 93 consecutive patients, 75 patients with no evidence of bleeding decreased their hematocrit level by 5.7% during their hospitalization.[10] Moreover, of the 64 patients who were not anemic on admission, 26 (40%) became anemic with no obvious cause at the time of discharge.[10] This finding shows the chronicity of this issue, yet it continues to be underrecognized decades later.

In the intensive care unit (ICU), about 90% of critically ill patients have a subnormal Hgb level by their third day of ICU admission.[11] Thus, anemia of critical illness is a common diagnosis in the ICU, and the prevalence of HAA in patients in the ICU is significant.

Surgical patients are known to be at high risk for development of HAA. The types of surgeries that are associated with major blood loss are cardiac, liver, orthopedic (major joints and spinal), craniofacial, and major urologic malignancy.[12] Many factors in addition to surgical blood loss contribute to the development of HAA in surgical patients.

Thus, the prevalence of HAA is significant from the wards, to the ICU, to surgical patients. If and when national reporting becomes mandated, it will be easier to obtain generalizable data and assess where we are as country in terms of prevalence of HAA.

2. Who is at risk for HAA?

An obvious question is whether it is possible to predict those patients at higher risk for developing HAA. Cardone and colleagues[12] and Welsby and colleagues[13,14] successfully developed prediction models to assess perioperative transfusion needs in orthopedic and cardiac surgery patients, respectively. Investigators have also looked at patients with acute myocardial infarction (AMI), critically ill patients in the ICU, and surgical patients from multiple subspecialties, with the goals of early recognition and prompt management of HAA.

Almost every patient who is admitted to a hospital is at risk of developing HAA, and those who are already anemic are at risk of worsening anemia during hospitalization. It seems reasonable to assume that the longer a patient stays at the hospital, the more likely the patient may develop HAA. Several studies do suggest correlation between the development of HAA and a longer length of stay, as well as with severity of illness

and Hgb level at the time of admission. Although there is no clear consensus about risk factors for HAA, most also agree that age older than 65 years and malnutrition are associated, as well.

3. What are the causes of HAA?

The cause of HAA is often multifactorial. The most common causes are repeat phlebotomy and blood loss from procedures, but other causes include gastrointestinal blood loss, decrease in production of erythropoietin (EPO), impaired bone marrow response, and reduced RBC survival. Critically ill patients lose about 25 to 40 mL of blood daily through phlebotomy alone, and patients with indwelling arterial catheters lose about 900 mL blood during their ICU stay.[11] It is hoped that these numbers have improved, given the increased awareness and number of solutions like reduced phlebotomy protocols, reinfusion kits, and improved techniques for arterial line placements. However, a more recent study is needed to definitively show improvement.

EPO resistance and the suppression of EPO production by gene inhibition are mediated by inflammatory mediators, like interleukin 1 (IL-1) and tumor necrosis factor α (TNF-α). In addition, TNF-α along with IL-6 and IL-1 suppresses erythropoiesis by direct inhibitory effects on bone marrow RBC production. There has been some suggestion that this effect can be reversed by exogenous EPO administration.[15] During sepsis syndrome, decreased RBC synthesis and development of anemia are common. Low serum iron levels and low total iron binding capacity with high ferritin concentrations in this setting suggest anemia of inflammation. Several studies have shown that bacteria require iron for growth and survival.[16–21] Thus, it seems as though downregulation of iron metabolism and EPO synthesis is a component of nonspecific immunity during critical illness and sepsis syndrome. As the human host tries to starve the pathogen of iron, the resulting anemia may be viewed as immune activation.

MANAGEMENT

1. Does the presence of HAA affect outcomes?

The most important sequela of anemia is the reduction in oxygen-carrying capacity of blood. This situation results in increased cardiac output, a shift of the oxyhemoglobin dissociation curve, and increased oxygen extraction, potentially reducing oxygen delivery at the tissue level. Presence of HAA in a variety of surgical and medical patients has been shown to worsen hospital and postdischarge outcomes. In orthopedic surgery patients, preoperative anemia and increased allogeneic blood transfusion (ABT) rates are both independently associated with increased risk of perioperative postoperative infections, increased hospital length of stay, and increased mortality.[22] In a retrospective cohort study of 227,425 noncardiac surgery patients, postoperative mortality at 30 days was higher in patients with anemia than in those without anemia (odds ratio 1.42, 95% confidence interval [CI] 1.31–1.54). This finding was consistent in mild and moderate to severe anemia.[23]

Attention has also been given to patients who suffer from AMI. Several studies have shown worse outcomes in patients who develop HAA after an AMI.[24–26] Salisbury and colleagues[8] identified 2909 patients with AMI who had normal Hgb levels on admission in the multicenter TRIUMPH (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status) registry and found that

at discharge 45.4% patients had HAA. After adjustments for GRACE (predictors of in-hospital mortality in the Global Registry of Acute Coronary Events) score and bleeding, patients with moderate to severe HAA (Hgb level <11 g/dL) had higher mortality (hazard ratio 1.82; 95% CI 1.11–2.98) than those with no HAA, and poorer health status at 1 year.

Hgb trajectories after discharge seem to influence outcomes in patients after myocardial infarction, both in those anemic on admission and those who develop de novo HAA. Salisbury and colleagues[27,28] found that patients with persistent HAA 1 month after discharge had lower health status scores than those with transient HAA. This gap remained at 6-month follow-up and narrowed again by 12 months, when no significant difference was observed. In addition, Anker and colleagues[29–48] found that declines in Hgb level at follow-up were associated with higher mortality, whereas increases in Hgb were associated with improved survival. This study differed from previously discussed studies, because the population investigated included patients who were already anemic at enrollment and then examined changes from baseline to 1-year follow-up.

A retrospective analysis of patients requiring prolonged acute mechanical ventilation[49] found that those patients who were transfused had worse clinical and economic outcomes. After adjusting for confounders, these investigators found an increase in the risk for hospital death, as well as increases in length of stay and cost of care.

2. What is the first step in the evaluation of a patient with HAA?

Once anemia is recognized in the hospital, it is crucial to investigate its cause. Is there an acute bleed, hemolysis, unrecognized hemoglobinopathy or malnutrition? These questions are critical, because management is determined by the cause of the anemia. A detailed history and physical examination are an essential first step and may prompt appropriate diagnostic imaging or endoscopic studies. If the cause of anemia remains unclear, suggested initial laboratory evaluation of patients with HAA is outlined in **Box 1**. The reticulated Hgb is a newer laboratory test, which, if readily available, can help with assessment of iron deficiency.

Results of these studies help determine if the patient is iron deficient or has another cause of anemia, such as anemia of chronic disease, hemolysis, chronic kidney disease, or other nutritional deficiencies.

Box 1
Laboratory evaluation of HAA

Serum Fe
Serum ferritin
Serum transferrin saturation (%)
Vitamin B_{12}/folate
Reticulocyte count: absolute and immature reticulocyte count (%)
Reticulocyte Hgb
Complete blood count with differential
Complete metabolic panel
Coagulation panel, disseminated intravascular coagulation panel, haptoglobin

3. After diagnostic studies, what is the next step in management of HAA?

The management of HAA can be divided into nonpharmacologic strategies and pharmacologic therapy (Fig. 1). Regardless of the cause of HAA, the next step is minimizing blood loss. The main nonpharmacologic strategy is to reduce blood draws, reduce unnecessary procedures, use Microtainers and smaller tubes (2-mL PediTubes) for necessary blood draws, stop any active bleeding, and hold any anticoagulants if there is a suspicion for a bleed.

The next step involves pharmacologic options. To start, one must begin with an assessment of iron, vitamin B_{12}, and folate levels and nutrition status. Use of these therapies is guided by the diagnostic evaluation. It is important to replace any recognized nutritional deficiencies, because this supports erythropoiesis. Malabsorption may impede the absorption of oral supplementation. Intravenous (IV) iron and EPO supplementation have shown benefit in select patients, and their use is detailed in Fig. 1.

4. What is the role of iron replacement in HAA?

Diagnosis of IDA

Most patients with HAA should be screened for iron deficiency anemia (IDA). Serum ferritin and transferrin saturation (TSAT) are considered the primary tools for assessing iron management in patients with anemia. The two main categories of IDA include absolute IDA and functional IDA. Table 2 summarizes the basic differences between absolute IDA and functional IDA.

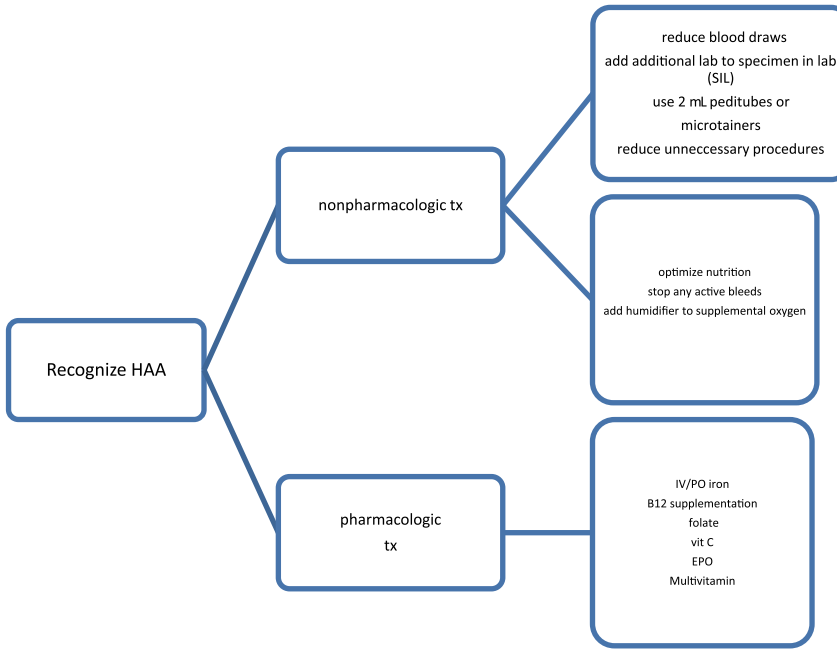

Fig. 1. Management of HAA.

Table 2
Summary of the basic differences between absolute IDA and functional IDA

IDA	
Absolute IDA	**Functional/Relative IDA**
Ferritin <100 ng/mL and TSAT <20%	Ferritin >100 ng/ml and TSAT >20%
Low or absent bone marrow staining for iron	No microcytosis or hypochromia

A ferritin of less than 10–15 ng/mL has a 55% sensitivity and 99% specificity for IDA. Given the low sensitivity, higher ferritin cutoff is reasonable. Thus, absolute IDA can be suspected if ferritin is less than 41 ng/mL. Ferritin has become the gold standard and replaced bone marrow staining.

Functional IDA is where iron is sufficient not deficient. The use of erythrocyte stimulating agents, phlebotomies, and blood loss will increase the erythropoiesis rate. The iron supply may be normal or increased and simply unable to be delivered rapidly enough to satisfy the iron need. Thus, iron deficient red blood cells are generated unless iron is supplied.

Oral Iron Replacement

Oral iron therapy suffices in many cases in which absorption is not an issue. This therapy is an inexpensive and effective means of restoring iron balance in most patients with IDA. To facilitate absorption, vitamin C is generally recommended (250-mg tablet or half a glass of orange juice daily), and one should wait about 2 to 4 hours after ingestion of antacids before taking oral iron. The choice of iron therapy may vary the amount of elemental iron (**Table 3**).

The recommended oral dose for the treatment of IDA in adults is 150 to 200 mg/d of elemental iron. The common prescription of 325 mg of iron sulfate 3 times daily delivers about 195 mg of elemental iron per day. No iron preparation is better than the others, and those that are enteric coated or sustained release may be poorly absorbed. Iron can be supplemented in the diet, as well. Examples of iron-rich foods include whole grains, liver, red meat, and dried beans, like kidney beans and lentils.

Typically, with moderate to severe anemia, reticulocytosis should be seen in 7 to 10 days, and this can be used to gauge adequate response to therapy. The Hgb concentration increases approximately 2 g/dL over 3 weeks after being treated for 1 to 2 weeks. There continues to be controversy as to how long to treat patients once the Hgb level normalizes. In cases in which there is either poor response to oral therapy, malabsorption, continued iron loss from a slow bleed, or intolerance to oral therapy, parenteral iron therapy may be considered (**Box 2**).

Iron Replacement

When considering IV iron therapy, in the United States there are 4 available iron products: ferumoxytol, ferric gluconate, iron dextran, and iron sucrose. The US Food and

Table 3
Choice of iron therapy and amount of elemental iron

Choice of Oral Iron Preparation	Amount of Elemental Iron (mg/tablet)
Ferrous fumarate	106
Ferrous sulfate	65
Ferrous gluconate	28–36

Box 2
Indications for parenteral iron therapy

Failed outpatient oral iron therapy with no change in Fe indices after 2 weeks of therapy

Excessive continuing blood loss

Malabsorption disorders (eg, inflammatory bowel disease, celiac disease, gastric bypass)

Chronic kidney disease

Cancer

Drug Administration (FDA) has delayed approval for ferric carboxymaltose, because of some concerns over hypophosphatemia and an imbalance of cardiovascular events and deaths. However, this agent is available in other countries. Iron isomaltoside is available in Europe, as well (Table 4).

Once the decision has been made to administer IV iron, each patient's iron deficit should be calculated to determine the appropriate dose. Several equations have been proposed to calculate the dosage of parenteral iron, but these 2 are the most commonly used:

1. Dose = 0.442 (desired Hgb level – observed Hgb level) × LBW + (0.26 × LBW), where LBW is lean body weight.
2. Dose = weight (kg) × (13 – current Hgb level) × 2.145.

Our institution uses the second one, given its simplicity.

The side effects of IV iron therapy include hypersensitivity reaction, hypotension, phlebitis, abdominal cramps, leg cramps, nausea, vomiting, and diarrhea. It is recommended that IV iron should not be given in the setting of an active infection, because iron may increase bacterial growth and virulence.

Table 4
Patients should be monitored for iron overload. Dosages listed here are for guidance and education only. The prescribing physician needs to adjust the dosage according to each clinical scenario

	Parenteral Iron Preparations			
	Iron Dextran	**Ferumoxytol**	**Ferric Gluconate**	**Iron Sucrose**
Test dose	Required 25 mg slow IV push and wait 1 h before giving remainder of dose	MD discretion	MD discretion 25 mg slow IV push or infusion	MD discretion 25 mg slow IV push
Dosage	100 mg IV over 5 min	Initial 510 mg IV injection, then second 510 mg IV injection 3–8 d later	125 mg IV over 60 min, dosage >125 mg not recommended. Total dose 1 g	200 mg IV over 60 min. Doses >300 mg not recommended
Routes	IV infusion	IV infusion	IV injection or infusion	IV injection or infusion

The FDA has approved iron sucrose for the treatment of IDA in patients with chronic kidney disease. Iron dextran is indicated in IDA and iron replacement for blood loss. In the August, 2009 FDA label, there is a dose calculation table for IDA and a calculation to estimate dosage of iron dextran when using this drug to replace iron in acute blood loss. It is important to review the adverse effects of these agents as well as the indication with the patient. It is important for the patient to be informed if the drug is being used outside FDA indications.

Iron studies should be rechecked 2 to 4 weeks after infusion. Thus, outpatient follow-up and communication between the discharging physician and the outpatient physician become important. Outpatient treatment regimens and follow-up are beyond the focus of this article.

5. What is the role of EPO in managing HAA?

Since the development of recombinant human EPO (rHuEPO), several cases have been reported in which rHuEPO was successfully administered in patients who refuse blood products. EPO, in combination with other blood conservation techniques, has been shown to increase Hgb levels and survival in patients who have experienced a gastrointestinal bleed, trauma, general surgery, cardiac surgery, orthopedic surgery, and burns.[50,51]

A multidisciplinary panel of physicians convened by the Network for Advancement of Transfusion Alternatives (NATA) in 2011 published practice guidelines for detection, evaluation, and management of perioperative anemia in the elective orthopedic patient.[52] In these guidelines, the benefit of oral iron, vitamin B_{12}, folic acid, and EPO to promote erythropoiesis was discussed. Erythrocyte stimulating agents were recommended when nutritional deficiencies have been corrected or ruled out. In addition, the 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines give the utilization of EPO plus iron in the preoperative setting a class IIa level B recommendation.[53]

The FDA has approved EPO for use in reducing ABT in preoperative patients with Hgb levels of 10 to 13 g/dL who are scheduled to undergo elective, noncardiac, and nonvascular surgery. The recommended dose is 300 units/kg subcutaneously daily, starting 10 days before surgery and continued until 4 days after surgery. Patients receiving EPO should receive concomitant iron, to optimize the Hgb response, as well as prophylaxis for deep venous thrombosis (DVT).

The rate of DVT is increased in surgical patients receiving EPO who do not receive pharmacologic prophylaxis, and chronic EPO use is associated with increased thrombotic cardiovascular events and increased mortality in patients with cancer and chronic kidney disease. EPO use should be restricted to approved indications, and potential risks and benefits should be discussed with the patient before treatment.

6. What is the role of transfusion in managing HAA?

See **Box 3** for indications for transfusion of packed RBCs (PRBCs) in anemic hospitalized patients. Detailed discussion of transfusion medicine is beyond the scope of this article.

New research continues to challenge the benefit of transfusing beyond a particular Hgb threshold. Examples in which active debate exists include the first 6 hours of sepsis management, when an Hgb level of 8 to 9 g/dL is believed to be optimal. In addition, for patients with cardiac disease or acute coronary syndrome, there is a suggestion to keep Hgb levels in the range of 8 to 9 g/dL. **Box 3** reflects the consensus of recommendations to date.

Box 3
Indications for transfusion of PRBCs in hospitalized anemic patients

Hgb level less than or equal to 7 g/dL

Symptomatic with Hgb level less than or equal to 8 g/dL (systolic blood pressure <80 bpm, heart rate >110 bpm not corrected by volume resuscitation, evidence of end-organ ischemia)

Acute coronary syndrome with Hgb level less than or equal to 8 g/dL and any 2 of the following: angina, new electrocardiographic changes, or abnormal enzymes

Acute massive blood loss of greater than or equal to 30% of estimated blood volume not corrected by volume resuscitation

Nonelective presurgery Hgb level less than or equal to 7 g/dL, with anticipated blood loss of greater than or equal to 750 mL

PREVENTION

1. Which strategies can prevent HAA?

Prevention of HAA begins in the office of the primary care physician. It is also the responsibility of the patient to enquire about their blood work and question any abnormalities. Early recognition and optimization of anemia before planned or unexpected hospitalization can prevent the development of HAA.

The second opportunity to prevent development or worsening of HAA falls to the admitting team. On admission, at-risk patients must be identified and the presence of anemia determined, the cause of the patient's anemia understood, and appropriate treatment opportunities sought. These results must be communicated to the rest of the treatment team, nurses, laboratory technicians, and other specialists involved in the case. The following is a list of the many ways in which HAA can be prevented:

- Magnets or signs can identify patients with or at risk for developing HAA who warrant conservative blood draws.
- Use protocols to assess iron stores once HAA is identified, and treat iron deficiency, if present.
- Use smaller tubes for blood draws (2-mL or 4-mL tubes).
- Use reinfusion kits.
- Reduce wasted blood after blood draws.
- Limit unnecessary procedures.
- Reduce hospital length of stay.
- Prevent unnecessary repeat laboratory testing.
- Identify coagulopathy and bleeding risk early.
- Use stress ulcer prophylaxis when indicated.
- Use order sets to ensure appropriate use of IV iron and EPO.

This effort requires a team approach, including hospital administration. It also requires a culture that supports fewer blood draws, conserving blood, and pursuit of treatment options to help prevent worsening anemia in the hospital. It truly is a multidisciplinary approach.

Given the complexities involved, establishment of a blood conservation team can help the institution with policy development and research and facilitate implementation of safe practices to prevent HAA.

PERFORMANCE IMPROVEMENT

1. Are there mandatory reporting requirements for HAA?

There is no mandatory reporting requirement for blood management programs in the United States. With the increasing attention given to HAA, it seems likely that quality measure(s) pertaining to HAA will be implemented in the near future. Several organizations, including the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), have published suggested guidelines to help blood management programs around the country to prepare their respective institutions for future quality requirements.

JCAHO has published *Patient Blood Management Performance Measures 2011*[54] as a guide for blood management programs in the United States. These performance measures include topics ranging from consent to blood administration documentation, preoperative screening, and blood product indications. These measures show the need to assess the existence of anemia before surgical procedures and the significance of establishing a culture in which recognition and treatment of HAA are second nature.

Other organizations like Society for the Advancement of Blood Management (SABM), American Association of Blood Banks (AABB), and NATA all have their own recommendations for reducing the incidence of HAA and avoiding transfusion.

Clinical Guidelines

Although there are no specific guidelines for HAA, helpful guidelines referenced above include:

AABB. Guideline published in *Annals of Internal Medicine*.[55]
KDOQI. Guideline published online at http://www.Kidney.org.
National Comprehensive Cancer Network. Guideline published online at http://www.nccn.org.

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