Measuring Total Hemoglobin 
Continuously and Noninvasively: 
An Up-to-the-Minute Approach

TARGET AUDIENCE This activity has been designed to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with elevated or decreased levels of hemoglobin.

STATEMENT OF NEED/PROGRAM OVERVIEW Anemia is often the first sign of a serious medical problem and it has been linked to poor outcomes in trauma as well as in many diseases. Abnormally high hemoglobin levels are associated with a higher risk of serious venous and arterial thrombosis. The ability to noninvasively monitor hemoglobin levels would be beneficial in clinical settings.

To obtain a total hemoglobin measurement via traditional routes requires drawing blood and sending samples to the laboratory for analysis. The results of these tests can take time to process. Clinicians must completely fill the collection tube and invert it several times to mix the blood sample and the anticoagulant, as well as handle the sample gently to prevent hemolysis. To specifically measure hemoglobin levels, a small quantity of blood must be analyzed in a hemoglobinometer. Although data is obtained within a few minutes, concentration levels have been shown to differ depending on where blood was drawn from.

Traditional hemoglobin diagnostics do not allow for continuous or noninvasive measurement of total hemoglobin. In surgeries associated with extensive blood loss, rapid fluid administration or transfusion, in emergency care situations, or in any instance where hemoglobin levels are rapidly changing, it has been noted that rapid, noninvasive measuring capabilities would be extremely beneficial for improving patient outcomes.

ACCREDITATION STATEMENT Physician Continuing Medical Education: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and Applied Clinical Education. PIM is accredited by the ACCME to provide continuing medical education for physicians.

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California Board of Registered Nursing: Postgraduate Institute for Medicine is approved by the California Board of Registered Nursing, Provider Number 13485 for 1.6 contact hours.

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LEARNING OBJECTIVES

At the completion of this activity, participants should be able to:

1. Describe the physiology of hemoglobin and its role in disease and anemia.
2. Explain elevated or decreased hemoglobin values, including the conditions that could contribute to such derangements.
3. Identify invasive and noninvasive technologies and methods that measure hemoglobin concentration and hematocrit levels.
4. Describe clinical scenarios in which hemoglobin concentrations would be rapidly changing, and where rapid or continuous measurement of hemoglobin concentration would be beneficial or necessary.
5. Outline how continuous monitoring of hemoglobin levels may affect clinical decision pathways and treatment outcomes.

DISCLAIMER Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient’s conditions and possible contraindications on dangers in use, review of any applicable manufacturer’s product information, and comparison with recommendations of other authorities.

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Introduction

Uncontrolled bleeding is a major cause of morbidity and mortality in the United States. Current methods to quickly quantify the severity of bleeding are insufficient to guide appropriate clinical decision-making and may contribute to poor outcomes in this population.

This article will briefly review the physiology and epidemiology of anemia and hemorrhage, discuss the current standards of care for the assessment of ongoing bleeding and acquired hemoglobinopathies, and review emerging technology for the continuous and noninvasive monitoring of hemoglobin (Hb) and hematocrit (Hct) levels in clinical populations.

Basic Physiology of Hemoglobin

The primary function of the circulatory system is to provide tissues with oxygen to facilitate cellular metabolism while simultaneously removing the by-products (eg, carbon dioxide). This role is fulfilled by the red blood cells (RBCs)—or erythrocytes—the majority of the cellular component of whole blood. Erythrocytes are anucleate cells that are rich in the oxygen transporter, hemoglobin.

The hemoglobin molecule is an assembly of 4 globular protein subunits attached to a non-protein iron-containing heme group that can reversibly bind oxygen and thereby participate in oxygen delivery to peripheral tissues. Thus, oxygen delivery is a function of RBC hemoglobin content as well as the percentage of RBCs contained within whole blood, a measurement known as the hematocrit.

The oxygen-binding properties of hemoglobin are dependent on several factors, one of which is the redox state of the iron molecule. Methemoglobin is a form of hemoglobin in which the iron in the heme group has been chemically oxidized from the normal Fe"2+ state to a Fe"3+ state. This change leads to abnormal oxygen affinity, reduced oxygen-carrying capacity, and tissue hypoxia. Methemoglobinemia can be induced by multiple pharmacologic and chemical exposures, and methemoglobin levels have been reported to be elevated in patients with sepsis as well as individuals with congenital metabolic anomalies such as glucose phosphate dehydrogenase deficiency. There have also been case reports of methemoglobinemia arising from the use of topical anesthetics, including lidocaine and benzocaine. Severe untreated methemoglobinemia can lead to hypoxia, organ damage, delirium, and death.

The toxic effects of carbon monoxide are also mediated by its ability to interfere with hemoglobin–oxygen binding. Carbon monoxide readily crosses capillary membranes in the lungs and binds to the heme moiety on the hemoglobin complex with an affinity 200 to 300 times greater than that of oxygen. This binding drastically decreases binding spots available for oxygen transport. Early symptoms of carbon monoxide poisoning are typically vague (eg, headache, dizziness, nausea) but can progress to loss of consciousness, permanent brain damage, and death.

Significance of Anemia, Polycythemia, and Acquired Hemoglobinopathies

Oxygen-carrying capacity is reduced in the context of decreased circulating hemoglobin or hematocrit levels (ie, anemia) as well as by acquired hemoglobinopathies (eg, methemoglobinemia, carboxyhemoglobinemia).

The normal hemoglobin value varies between individuals. The level of reduction in hemoglobin or hematocrit levels that constitutes significant anemia remains a topic of controversy. For example, if anemia is defined as values that are more than 2 standard deviations below the mean, then an Hb <13.5 g/dL and <12 g/dL or an Hct <41% and <36% represents anemia in men and women, respectively. By contrast, criteria reported by the World Health Organization in 1968 define anemia in men and women as Hb <13 and <12 g/dL, respectively. However, a review of the range of “normal” hemoglobin values suggests that the definition of normal values is likely more complex and may by dependent on other variables, including age and race.

Anemia is the most common hematologic disorder in the United States, where it affects more than 3 million people of all ages and ethnicity. Several populations appear to be particularly vulnerable to the development of anemia: The Centers for Disease Control estimate that 7% of children ages 1 to 2, and...
between 9% and 16% of women between the ages of 12 and 49 have iron-deficiency anemia. Furthermore, a study of the US population found that 12% of white women were estimated to be iron deficient compared with 22% of women from Mexican American decent and 19% of black women. Geriatric patients are also at risk for anemia; according to data from the third National Health and Nutrition Examination Survey (1988-1994), approximately 10% of people 65 years of age or older are anemic. When severe, anemia can lead to fatigue, tachycardia, and poor exercise tolerance, and can adversely affect outcomes in a variety of medical conditions. For example, maladaptive cardiac compensation in response to longstanding anemia can lead to high-output congestive heart failure and irreversible remodeling of the myocardium. Other studies have demonstrated that even mild anemia has substantial ramifications as a comorbid factor for other illnesses, as well as serious implications of its own. In general, patients with anemia have shorter life spans compared with same-age peers without anemia. Anemia also represents an important risk factor for mortality in patients with HIV, cancer, renal disease, patients undergoing dialysis, and patients with heart disease.

One review by Knight and colleagues found that, depending on the definition of anemia, between 30% and 90% of patients with cancer were anemic and that they had poorer survival and local tumor control compared with patients without anemia. For patients undergoing elective surgeries, the prevalence of anemia has been estimated to be as high as 75% in certain populations. Lower pre- and postoperative hemoglobin levels have also been found to result in longer lengths of hospital stays, with higher odds of readmission or death within 60 days of discharge. One study by Nissenson and colleagues evaluating administrative medical claims by more than 2.3 million managed care health plan members found that the costs for patients with anemia were more than twice the adjusted cost of patients without anemia with the same comorbid conditions. The etiologies of anemia are multiple, but can be generally subdivided into the categories of decreased RBC production (eg, nutritional deficiencies, bone marrow disorders, absence of growth factor production in the context of chronic renal failure), increased RBC destruction (eg, inherited disorders, acquired hemolytic anemias), and acute and chronic blood loss. Blood loss may take any one of a number of forms, including obvious bleeding (eg, trauma, melena, hematemesis, hemorrhage during child delivery), occult bleeding (eg, bleeding ulcer or carcinoma), or induced bleeding (eg, repeated diagnostic testing, hemodialysis losses, excessive blood donation, intraoperative bleeding).

Chronic forms of anemia are treated by correcting any reversible factors and by assuring a proper environment for generation of new RBCs. This typically consists of nutritional supplements (eg, folate, vitamin B12, iron) when appropriate or administration of growth factors (eg, erythropoietin, darbepoetin) in patients with anemia associated with chronic kidney disease or cancer. Trauma-related hemorrhage remains a leading cause of death in civilian and military personnel. Severe anemia resulting from acute blood loss is associated with a high and immediate risk of morbidity and mortality and requires aggressive management. General treatment strategies for the patient with acute blood loss include fluid support with crystalloid solutions; transfusion of RBCs; efforts to terminate bleeding by surgical, endoscopic, or intravascular means (ie, intravascular embolization); and enhancement of inherent hemostatic mechanisms with prothrombogenic agents. However, all of these strategies can be associated with significant morbidity (Table 1). For example, blood transfusions can provoke allergic or hemolytic reactions, carry a risk of transmission of infectious agents, and require tremendous resources (eg, obtaining and testing blood products, patient monitoring during infusion). Additionally, long-term administration of RBCs for those with

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<th>TABLE 1. RISKS AND DISADVANTAGES ASSOCIATED WITH DIFFERENT TREATMENTS FOR ACUTE OR SUBACUTE BLOOD LOSS</th>
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<td><strong>Surgery</strong></td>
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TABLE 2. CLINICAL SCENARIOS THAT MAY BENEFIT FROM NONINVASIVE AND/OR CONTINUOUS MONITORING OF HEMOGLOBIN OR ACQUIRED HEMOGLOBINOPATHIES

- First-responder situations (triage)
- Gastrointestinal bleed
- Hemodialysis
- Hemorrhage during child delivery
- Intensive care unit patients
- Induction chemotherapy/neutropenic patients
- Interhospital transport of critical patients
- Massive hemoptysis
- Patient with religious objection to receiving blood products
- Retropertioneal bleed
- Surgical patients (intraoperative and postanesthesia care unit)
- Suspected smoke inhalation
- Industrial toxic exposure
- Suspected carbon monoxide exposure
- Trauma

chronic disorders can result in end-organ damage from iron overload. Finally, administration of large volumes of blood products or crystalloid solution may provoke congestive heart failure in vulnerable populations.

The other intervention-based modes of management are invasive and can be associated with a significant degree of morbidity and mortality. For example, emergent surgery to achieve hemostasis is associated with a relatively high risk of complications and postoperative morbidity and mortality, and is typically used as a strategy of last resort.

By contrast, an increase in red cell mass or erythrocyte number beyond the normal range is known as polycythemia. This condition can either be primary (ie, resulting from an acquired or inherited mutation expressed within erythroid progenitors) or, more commonly, secondary. Secondary polycythemia results from conditions in which there are circulating plasma factors that stimulate erythropoiesis. This can occur in the context of chronic hypoxic conditions (eg, chronic obstructive pulmonary disease, congenital heart disease) or the administration of excessive amounts of exogenous erythropoietic factors (eg, erythropoietin, darbepoetin) in those with chronic kidney disease (CKD). As a result of increased blood viscosity related to increased erythrocyte numbers, patients with polycythemia are a higher risk of developing thrombosis or thromboembolic disease, which can result in significant morbidity and mortality.

Because both low and high hemoglobin levels may be associated with worse outcomes relative to normal hemoglobin values, several studies have attempted to determine the optimal hematocrit and hemoglobin levels for patients with CKD undergoing treatment with erythropoietin. The CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial randomly assigned 1,432 patients with CKD to achieve a target hemoglobin level of either 13.5 or 11.3 g/dL. The CHOIR study was terminated early (at a median duration of only 16 months) because there was less than a 5% chance of demonstrating a relative cardiovascular benefit in the high hemoglobin group. Another reason for early termination included a significantly higher number of adverse events (AEs) in the high hemoglobin arm (125 vs 97 AEs; hazard ratio [HR] 1.34; 95% confidence interval [CI], 1.03-1.74). This difference resulted primarily from nonsignificant trends in the high hemoglobin group for an increased risk of death (52 vs 36 deaths; HR 1.48; 95% CI, 0.97-2.27) and hospitalization for heart failure (64 vs 47 AEs; HR 1.41; 95% CI, 0.97-2.05). Both arms showed similar improvement in quality of life measures.

Further, the CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta) trial randomly assigned 603 patients with CKD and anemia to achieve a target hemoglobin level of either normal (13-15 g/dL) or subnormal (10.5-11.5 g/dL). The primary end point was a composite of 8 cardiovascular events, including sudden death, myocardial infarction, acute heart failure, stroke, transient ischemic attack, hospitalization for angina pectoris or arrhythmia, or complications of peripheral vascular disease. At 3 years, a similar risk of experiencing the primary endpoint was observed in both groups (HR 0.78; 95% CI, 0.53-1.14). Both arms also had similar changes in left ventricular mass and rates of progression of CKD. Increased general health and enhanced quality of life were observed in the high hemoglobin group.

In terms of acquired hemoglobin dysfunction, carbon monoxide poisoning is the most common type of accidental poisoning in the United States, accounting for thousands of emergency department visits and between 5,000 and 6,000 deaths per year. Several studies suggest that carbon monoxide poisoning is underdiagnosed and that cases of unrecognized carbon monoxide poisoning may be present in patients who are hospitalized for other medical problems. Methemoglobinemia is much less common than carbon monoxide poisoning but can be equally devastating. Most cases are acquired and result from exposure to drugs or toxins. Two of the more common causes are exposure to topical benzocaine and dapsone. An estimated 0.115% of patients undergoing transesophageal echo with topical benzocaine administration develop methemoglobinemia. The incidence of methemoglobinemia in response to benzocaine and other agents is not known.

Current Assessment of Blood Loss or Altered Oxygen-Carrying Capacity

Because of the risks of polycythemia or acute blood loss and its associated treatments, rapid estimation of the degree of anemia may help determine which patients would benefit from

TABLE 3. ADVANTAGES OF OXIMETER-BASED ASSESSMENT OF HEMOGLOBIN, HEMATOCRIT, AND ACQUIRED HEMOGLOBINOPATHIES OVER CONVENTIONAL TECHNIQUES

| Continuous measurement allows for real-time assessment of critical patients |
|-----------------------------|-----------------------------|
| Less expensive              | No disposable reagents      |
|                             | No need for secure disposal of biohazardous material |
|                             | Minimal training required   |

| Less invasive               | No need for venipuncture or arterial puncture |
|                            | No risk of inadvertent needle sticks |
|                            | Less time-consuming |

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<th>May be suitable as an inexpensive and rapid screening test</th>
<th>Chronic anemia</th>
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<td>Portable</td>
<td>Occult carbon monoxide poisoning</td>
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<td>Allows bedside evaluation</td>
<td>Suitable for use by first-responders or during transport</td>
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aggressive intervention while simultaneously avoiding high-risk procedures in those patients who require only conservative treatment. Furthermore, because the symptoms of carboxyhemoglobinemia and methemoglobinemia are nonspecific and vague, a simple and accurate way to screen for these disorders may result in improved accuracy of diagnosis and improved outcomes in these patients (Table 2).

Assessment of patients with critical intravascular volume depletion resulting from acute blood loss is achieved through a combination of vital sign analysis and laboratory testing, with supplementary data provided by clinical history, physical examination, and occasionally, radiographic testing. The chief component of laboratory testing in this regard is baseline and serial assessment of hemoglobin or hematocrit levels. The majority of routine and urgent testing of hemoglobin value in the inpatient setting is performed via a central laboratory. The test is usually part of a “complete blood count” and requires venipuncture and aspiration of 5 to 10 mL of blood into a glass tube containing a small amount of anticoagulant, which is subsequently transported to the laboratory for processing.

This procedure is associated with significant disadvantages (Table 3). For example, improperly mixing the blood with an anticoagulant can render the sample unusable, improper handling can lead to hemolysis and falsely low readings, and prolonged use of a tourniquet can result in hemoconcentration and false elevated readings. Serial monitoring also requires repeat venipuncture, which results in patient discomfort, a risk of inadvertent needle sticks, and increased exposure of immunosuppressed individuals (eg, those receiving induction chemotherapy) to potential pathogens. Because laboratory blood analysis requires disposable reagents, secure disposal of biohazard material, and the use of trained personnel (eg, phlebotomist, laboratory technicians), the overall cost is relatively high. Finally, although the laboratory apparatus can typically process samples within minutes, the multistep procedure needed to obtain and transport the specimen means that results are rarely available in less than 30 minutes.

**Figure 1. Absorption Spectra of Hemoglobin and Oxyhemoglobin**

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**Technologies for the Continuous and Noninvasive Assessment of Hematologic Parameters**

Based on the limitations of traditional techniques, investigators have employed several different types of technologies, including those measuring electrical, acoustic, and optical properties of blood, in an attempt to continuously and noninvasively measure intravascular hemoglobin levels and to screen for acquired hemoglobinopathies. The majority of devices currently in development rely on optical methods.

**Electrical**

Impedance plethysmography is a technique in which small electrical currents are applied to the skin; voltage response to the current is measured and used as an indicator of blood volume. This type of testing has been used to estimate cardiac stroke volume and also as an indicator of potential peripheral venous thrombosis. However, clinical application of this technique has been limited by poor sensitivity and specificity.

Similar electrical methods have been employed for the noninvasive analysis and quantification of hematocrit levels in vivo. Most protocols involve stimulation of the finger with simultaneous high- and low-current electrical frequencies; induced voltages are then captured and separated into baseline and pulsatile components, and a mathematical algorithm is used to calculate the hematocrit component based on prior modeling and standardized curves.

Although development of this technique for noninvasive monitoring of hematocrit levels has not achieved widespread acceptance, some recent investigators have reported success with measurement of hematocrit levels in an extracorporeal circuit. Ishihara and colleagues used this technique to measure hematocrit levels in the arterial efflux circuit during hemodialysis and reported good concordance between levels measured noninvasively and those obtained via traditional ex vivo methods. Furthermore, they reported that use of continuous hematocrit data allowed for adjustment of ultrafiltration parameters to minimize adverse effects, such as hypotension associated with dialysis. However, as with the use of impedance plethysmography for the evaluation of total blood volume or venous thrombosis, the sensitivity and specificity of this technique is not currently sufficient to accurately measure hematologic parameters in vivo.

**Acoustic**

Ultrasonography with and without Doppler analysis is a noninvasive method that is already employed in a wide range of medical applications, from obtaining structural organ data to estimating arterial and venous blood flow. This technology is based on the continuous measurement of acoustical impedance, in which sound waves are emitted from a transducer on the skin surface and then reflected back to a sensor when they encounter changes in acoustic density. Several investigators have postulated that modification of this method could allow continuous and noninvasive quantification of total protein concentration in peripheral arteries and that this measurement could be extrapolated to calculate circulating hemoglobin levels.

When Johner and colleagues utilized an ultrasound-based protocol for the measurement of blood volume, they incidentally reported that the device enabled measurement of hematocrit and hemoglobin levels. A comparison with conventional methods revealed that ultrasound-based assessment of hematocrit was accurate to within 2.9% of the hematocrit level and 0.8 g/dL of the hemoglobin level.

A more recent study by Secomski and colleagues used Doppler methods and complex gating with a different mathe-
optical algorithm and reported that hematocrit could be noninvasively determined from imaging the brachial artery to within an error of 5%. However, even small lateral movements of the image significantly limited the technique, thus making it impractical for continuous use in the clinical setting. Other problems included the need for large and expensive machinery and accuracy that tends to be highly dependent on operator expertise.\textsuperscript{66,67}

**Optical**

Another method for continuous and noninvasive measurement of hemoglobin and hematocrit is near-infrared spectrophotometry (NIRS), and relies on the principles of optical radiation and absorption.\textsuperscript{70} This technology has been demonstrated in association with pulse oximetry. This allows noninvasive measurement of arterial hemoglobin saturation without the risks associated with arterial puncture, and some investigators have used similar methods for real-time measurement of blood glucose levels in patients with diabetes,\textsuperscript{71,72} deep tissue pH in muscle,\textsuperscript{73} and levels of methemoglobin and carboxyhemoglobin.\textsuperscript{74-76}

The theoretical basis of NIRS derives from the Beer-Lambert law. This law states that the extinction of a given wavelength of light passing through a nonabsorbing solvent containing an absorbing solute is proportional to the product of the solute concentration, the light path length, and an extinction coefficient.\textsuperscript{77} Application of this spectrophotometric principle to a practical device, where tissue is of varying thickness and blood flows in a pulsatile manner, is more complicated. Modern pulse oximeters address these factors through simultaneous use of multiple wavelengths and sophisticated microprocessors. Deoxyhemoglobin absorbs light maximally in the red band of the spectrum (600-750 nm), whereas oxyhemoglobin absorbs maximally in the infrared band (850-1,000 nm; Figure 1).\textsuperscript{78-80} The relative absorbance at these 2 wavelengths is used in standard pulse oximeters to estimate oxygen saturation, which is derived from the ratio of oxyhemoglobin to the sum of oxyhemoglobin plus deoxyhemoglobin.\textsuperscript{81,82}

Because all forms of hemoglobin have strong absorption bands in the spectral region of 500 to 1,100 nm,\textsuperscript{70} the combination of absorption spectra at multiple wavelengths and subsequent processing by mathematical algorithms can also enable calculation of total hemoglobin levels. Indeed, several commercial prototypes have been developed that measure hemoglobin levels based on NIRS.

**Clinical Data With Commercial Prototypes**

**Extracorporeal Monitoring**

Accurate dry-weight assessment is difficult in hemodialysis patients but is essential to prevent adverse effects while simultaneous preventing fluid accumulation during dialysis. Although not technically noninvasive, several different commercial technologies have been utilized for the continuous ex vivo monitoring of hematocrit as a proxy for other cardiovascular parameters. For example, the CRIT-LINE\textsuperscript{®} instrument (Hema-Metrics, Kaysville, UT) uses optical absorption to continuously calculate the hematocrit in the arterial efflux circuit during hemodialysis. Because the total number of RBCs is presumed to remain relatively constant during dialysis, any changes in hematocrit will be inversely proportional to changes in the blood volume and can help guide ultrafiltration parameters to assure that the rate of fluid removal is appropriate.

Patel and colleagues\textsuperscript{83} studied this system in 20 pediatric hemodialysis patients. Based on information from the CRIT-LINE system, the investigators created an algorithm whereby the first 50% of total ultrafiltration volume was removed during the first hour and the remaining volume was removed over the remaining treatment period of 2 to 3 hours). The investigators reported that the use of this system was associated with better post-dialysis blood pressure control, decreased need for anti-hypertensive medications, and a decreased rate of adverse events (eg, hypotension) related to ultrafiltration.

Steuer and colleagues\textsuperscript{84} also studied the utility of the CRIT-LINE system in dialysis patients and reported that predictable symptoms occurred at a patient-specific hematocrit. Based on these data, they set ultrafiltration rates to maintain the instantaneous hematocrit value 2 units below the established hematocrit threshold and compared outcomes with patients who did not receive ultrafiltration rate adjustments based on hematocrit. The investigators reported that the frequency of adverse effects (eg, lightheadedness, cramping, and nausea) was significantly lower in those patients who underwent hematocrit-guided adjustments in ultrafiltration relative to those who did not (26% vs 57%). Similar results in response to CRIT-LINE-assisted ultrafiltration protocol have also been reported.\textsuperscript{85}

However, Reddan and colleagues\textsuperscript{86} performed a randomized trial of ultrafiltration adjustments and interventions based on the CRIT-LINE system compared with conventional clinical monitoring. Surprisingly, the investigators reported that mortality was significantly higher in the CRIT-LINE group than in the conventional monitoring group (8.7% vs 3.3%). Furthermore, hospitalization rates were also higher in the CRIT-LINE group (1.51 and 1.03 events per year, respectively). The investigators noted that these findings were at odds with previous reports and suggested that the higher rates of hospitalization may have resulted from the high degree of vigilance in those receiving CRIT-LINE monitoring. They could not account for the higher rates of mortality in the CRIT-LINE group. Thus, the advantage of CRIT-LINE monitoring in patients undergoing hemodialysis and ultrafiltration treatments remains unproven.

**In Vivo Optical-Based Monitors**

Several prototype commercial devices based on optical NIRS technology have been developed for the continuous and noninvasive measurement of hemoglobin and hematocrit, including the Astrim\textsuperscript{™} monitor (Sysmex Corporation, Kobe, Japan), the NBM-100 monitor (Orsense Ltd., Nes Ziona, Israel), and the Rainbow SET\textsuperscript{™} CO-oximeter (Masimo Corporation, Irvine, CA).

**Astrim Monitor**

In 1999, the Sysmex Corporation developed the Astrim monitor, a device to measure hemoglobin using a near-infrared emitting source (3 wavelengths of 660, 805, and 880 nm) and a charge-coupled device camera that are applied to opposing sides of a finger.\textsuperscript{87,88}

Kanashima and colleagues\textsuperscript{89} studied the accuracy of the Astrim monitor by measuring hemoglobin levels in 140 subjects and comparing values with those obtained by standard techniques. The investigators reported that measurement of hemoglobin levels by these two techniques corresponded with a correlation coefficient of $r = 0.591$. Furthermore, this correlation held when patients were subdivided on the presence or absence of anemia. However, the diagnostic sensitivity and specificity of the Astrim monitor for anemia based on these data was 78.3% and 69%, respectively, which is not sufficient for use in routine screening. The authors attributed this suboptimal sensitivity and specificity to variables in the measurement conditions (ie, the finger selected for measurement,
the finger position in relation to the camera, and the finger temperature.

**NBM-100 Monitor**

Another noninvasive device is the NBM-100 monitor. This device also uses sensitive red/near-infrared spectrophotometry, although the precise wavelength on which this device operates has not been described in the literature. The device also employs blood-flow occlusion to yield a more favorable signal-to-noise ratio in response to the optical readings. Specifically, a ring-shaped pneumatic cuff and sensor is fitted on the patient’s finger, and the ring gently pressurizes the finger to over-systolic pressure, in a process similar to that of the conventional blood pressure cuff90 (Figure 2).

Kononenko and colleagues91 studied the utility of the NBM-100 monitor in 10 patients in the intensive care unit or the postanesthesia care unit. The NBM-100 probe was applied to the patients’ thumbs, and data were recorded every 10 to 15 minutes for periods ranging from 2 to 12 hours. In order to compare the data to conventional techniques, arterial blood samples were obtained every 30 to 60 minutes to measure hemoglobin levels. The investigators reported that the NBM-100 monitor was able to successfully record hemoglobin trends with a mean absolute error of 1 g/dL. Furthermore, the device retained its accuracy over a wide range of hemoglobin values, which the investigators noted would be a particularly valuable property for patients experiencing hemorrhage and rapid blood dilution as a result of administration of intravenous fluids.

Berrebi and colleagues92 subsequently tested this apparatus in 304 subjects in a blood donation center and an outpatient hematology clinic. All patients also underwent venipuncture for conventional measurement of hemoglobin and hematocrit. The investigators reported that the operating staff at all centers found the NBM-100 easy to use and that study participants were generally appreciative of the noninvasive technique. Furthermore, the standard deviation of the difference between the 2 types of reading was 3.3%, and the bias between the 2 methods was 0.40%, resulting in a correlation coefficient of 0.9.

Other studies by Monashkin and colleagues93 have reported that this apparatus can simultaneously provide accurate data regarding the oxyhemoglobin-to-deoxyhemoglobin ratio.

**Rainbow SET CO-Oximeter**

The Masimo Corporation has also developed a prototype pulse CO-oximeter designed to continuously and noninvasively measure hemoglobin concentration using a finger probe94 (Figure 3). The finger probe uses multiple proprietary wavelengths but is mechanically similar to a standard pulse oximeter probe.

Macknet and colleagues95 tested the utility of this device in 30 patients scheduled to undergo surgery, as well as in 18 healthy volunteers. Volunteers underwent a hemodilution protocol that consisted of withdrawal of 1 unit of blood and replacement with 30 mL/kg of saline. Data was collected intraoperatively and during the hemodilution protocol, and arterial blood samples were also obtained for conventional measurement of hemoglobin. The investigators reported that the oximeter measured hemoglobin values over a range of 4.4 to 15.8 g/dL with a bias of 0.03 and a precision of 1.12. Hemoglobin measurements between the 2 methods correlated well ($r = 0.882$; Figure 4).

Macknet and colleagues96 also used the device for the continuous measurement of hemoglobin levels in a 65-year-old female undergoing liver transplantation. Data were collected with the oximetry monitor throughout the course of the surgery, and arterial blood samples were obtained at least every hour for conventional hemoglobin measurements. Over the 16.6-hour procedure, continuous monitoring recorded a range of hemoglobin values (Hb 5.8-10.3 g/dL) with a bias of 0.146 and a precision of 0.740. The investigators further reported they were able to tell the anesthesiologist when to check hemoglobin concentration because the device was
reporting critical values. The investigators believe that continuous monitoring of hemoglobin with the prototype device will facilitate clinical decision-making during times of rapidly changing hemoglobin concentration related to surgical blood loss and transfusion.

Variants of NIRS also allow for real-time measurement of hemoglobinopathies. Barker and colleagues conducted a study that utilized an 8-wavelength Rad-57 pulse CO-oximeter developed by the Masimo Corporation to measure methemoglobin and carboxyhemoglobin levels. Ten volunteers breathed carbon monoxide until their carboxyhemoglobin levels reached 15%, and intravenous sodium nitrite was administered to 10 other volunteers to induce methemoglobinemia. When compared with conventional measurements via arterial blood sampling, the Rad-57 CO-oximeter measured carboxyhemoglobin levels with a precision of ±2% and methemoglobin with a precision of 0.5%.

Implications for Clinical Decision-Making

A significant amount of resources are needed for assessment of volume status and anemia in the critically ill patient, most often consisting of serial blood sampling, which is time-consuming, painful, and costly. The ability to measure hemoglobin, and hemoglobinopathies noninvasively in real time may improve the accuracy and speed of diagnosis as well as reduce the cost and complications associated with invasive alternatives. If additional clinical studies validate these devices for the accurate and reproducible assessment of hemoglobin levels, the new monitors may even replace venipuncture and conventional measurements of hemoglobin for screening purposes in the outpatient setting or emergency room. These monitors also have the potential to provide first-responders, such as paramedics and firefighters, with a rapid determination of hemoglobin and hemoglobinopathies resulting from trauma and toxic exposure in the field.

Regardless of their potential, these devices do suffer from limitations. First, hemoglobin levels during severe acute hemorrhage may be normal or even increased because of the inherent lag time in body fluid shifts and may result in a delayed recognition and initiation of fluid and blood replacement. Second, there have been no studies to demonstrate that continuous and noninvasive monitoring of hemoglobin results in improved outcomes for patients. Indeed, studies of continuous extracorporeal monitoring to guide treatment decisions in patients undergoing dialysis showed a disappointing increase in mortality rate for those who were continuously monitored. Thus, further study is required to determine the role of these new devices in clinical decision-making.

FIGURE 4. CORRELATION BETWEEN HEMOGLOBIN VALUES ASSESSED BY MULTI-WAVELENGTH CO-OXIMETER (SpHb) (MASIMO CORPORATION) AND CONVENTIONAL METHODS (HBT)

Reprinted with permission from reference 96.
CME/CE/CPE Post-test

Choose the single letter response that best answers the question or completes the sentence.

1. Which of the following statements regarding hemoglobin is TRUE?
   a. Hemoglobin is composed of four globular proteins and a heme moiety
   b. Hemoglobin is localized in the red blood cell nucleus
   c. Hemoglobin irreversibly binds to oxygen
   d. All of the above

2. Secondary polycythemia results from ______.
   a. acquired or inherited mutation expressed with erythroid progenitors
   b. conditions in which circulating plasma factors stimulate erythropoiesis
   c. carbon monoxide intoxication
da. all of the above
3. All of the following statements regarding methemoglobinemia are true, EXCEPT:
   a. Methemoglobinemia results from conversion of the iron in the heme moiety from the Fe²⁺ state to the Fe³⁺ state
   b. Methemoglobinemia is associated with increased oxygen delivery to peripheral tissues
   c. Methemoglobinemia can be induced by various drugs
   d. Methemoglobinemia can result from a congenital metabolic abnormality

4. The hemoglobin/hematocrit parameters that define anemia may vary with which of the following factors?
   a. Gender
   b. Race
   c. Age
   d. All of the above

5. According to data from the third National Health and Nutrition Examination Survey, what is the prevalence of anemia in people 65 years or older?
   a. 0.1%
   b. 1%
   c. 10%
   d. 30%

6. Which of the following disadvantages is associated with transfusion of red blood cells?
   a. Allergic reactions
   b. Potential to transmit infectious agents
   c. Potential to provoke congestive heart failure
   d. All of the above

7. Which of the following agents can induce formation of methemoglobin?
   a. Isoflurane
   b. Benzocaine
   c. Midazolam
   d. Fentanyl

8. According to the Centers for Disease Control, iron-deficiency anemia is most prevalent in women of what race/ethnicity?
   a. African Americans
   b. Asian Americans
   c. Caucasian Americans
   d. Mexican Americans

9. Which of the following statements regarding standard hemoglobin/hematocrit testing via venipuncture and processing by a central laboratory is TRUE?
   a. Results are typically available within 5 minutes
   b. Hemolysis due to improper handling results in falsely elevated hematocrit values
   c. Prolonged use of a tourniquet can result in hemoconcentration and falsely elevated readings
   d. All of the above

10. All of the following statements regarding commercial prototype monitors for the continuous and noninvasive monitoring of hemoglobin are true, EXCEPT:
    a. These devices may provide a viable option for assessment by first-responders
    b. These devices may allow the simultaneous assessment of hemoglobin levels, arterial oxygen saturation, and pulse
    c. These devices may enable simple and inexpensive screening for occult carboxyhemoglobin toxicity
    d. These devices have been shown to improve patient outcomes in randomized studies

11. Which of the following statements regarding ultrasound-based continuous monitoring of hemoglobin and hematocrit is TRUE?
    a. The technique is highly operator-dependent
    b. The technique is highly accurate when used for ambulatory monitoring
    c. The technique is inexpensive
    d. All of the above

12. Optical-based continuous and non-invasive monitoring of hemoglobin and hematocrit relies on which of the following principles?
    a. Impedance plethysmography
    b. Acoustical impedance
    c. Beer-Lambert’s law of spectrophotometric absorbance
    d. None of the above

13. During which of the following clinical scenarios would a patient potentially benefit from continuous and noninvasive monitoring of hemoglobin and hematocrit?
    a. Massive gastrointestinal bleeding
    b. Liver transplantation
    c. Multiple trauma
    d. All of the above

14. Which of the following statements regarding the use of the CRIT-LINE™ hematocrit monitor-guided treatment decisions during dialysis and ultrafiltration is TRUE?
    a. Monitor-guided treatment algorithms resulted in decreased dizziness and nausea during ultrafiltration
    b. Monitor-guided treatment algorithms resulted in the need for a greater number of antihypertensive medications to control blood pressure in between dialysis sessions
    c. Monitor-guided treatment algorithms resulted in lower rates of mortality
    d. Monitor-guided treatment algorithms resulted in lower rates of hospitalization

15. Prototype CO-oximetry monitors may allow continuous and noninvasive measurements of which of the following?
    a. Hemoglobin levels
    b. Carboxyhemoglobin levels
    c. Methemoglobin levels
    d. All of the above
EVALUATION FORM
Measuring Total Hemoglobin Continuously and Noninvasively: An Up-to-the-Minute Approach
Project ID: 4986-ES-34

Postgraduate Institute for Medicine (PIM) respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment of participation for this activity.

Please answer the following questions by circling the appropriate rating:

1 = Outstanding 2 = Good 3 = Satisfactory 4 = Fair 5 = Poor

**Extent to which program activities met the identified purpose and objectives**
The purpose of this educational monograph is to explain clinical scenarios in which hemoglobin concentrations rapidly change, identify invasive and noninvasive methods that measure hemoglobin concentration and hematocrit levels, and discuss how continuous monitoring of hemoglobin levels has the potential to improve patient care and safety during surgical procedures.

Upon completion of this activity, participants should be better able to:

- Describe the physiology of hemoglobin and its role in disease and anemia.
- Explain elevated or decreased hemoglobin values, including the conditions that could contribute to such derangements.
- Identify invasive and noninvasive technologies and methods that measure hemoglobin concentration and hematocrit levels.
- Describe clinical scenarios in which hemoglobin concentrations would be rapidly changing, and where rapid or continuous measurement of hemoglobin concentration would be beneficial or necessary.
- Outline how continuous monitoring of hemoglobin levels may affect clinical decision pathways and treatment outcomes.

**Overall effectiveness of the activity**
Was timely and will influence how I practice
Fulfilled my educational needs
Avoided commercial bias or influence

**Impact of the activity**
The information presented: (check all that apply)
- Reinforced my current practice/treatment habits
- Will improve my practice/patient outcomes
- Provided new ideas or information I expect to use
- Enhanced my current knowledge base

Will the information presented cause you to make any changes in your practice? Yes No
If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

**Follow-up**
As part of our ongoing continuous quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:
- Yes, I would be interested in participating in a follow-up survey
- No, I’m not interested in participating in a follow-up survey

Additional comments about this activity:
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**Post-test Answer Key:**
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3. a b c d  8. a b c d  13. a b c d
4. a b c d  9. a b c d  14. a b c d
5. a b c d  10. a b c d

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Do you feel future activities on this subject matter are necessary and/or important to your practice? Yes No
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