# Iatrogenic anemia - a downside of blood testing

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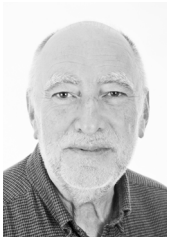

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All clinical procedures and treatments are associated with potential adverse effects of greater or lesser significance.

The undisputed value of blood testing for both diagnosis and monitoring of disease is tempered by the recognition that repeated blood sampling can result in blood loss of sufficient magnitude to cause anemia that may contribute to the necessity for red-cell transfusion in particular patients.

This adverse effect of laboratory testing, often referred to as either iatrogenic (physician-induced) anemia or nosocomial (hospital-acquired) anemia, is the subject of this article.

Consideration will be given to the extent of blood loss due to blood sampling among hospitalized patients, as well as some of the physiological and pathological factors that determine if that blood loss has clinical effect. Strategies aimed at minimizing the blood loss associated with laboratory testing will be discussed.

## Blood loss due to laboratory testing in adults

In the early 1970s, physicians working in the coronary care unit (CCU) of a New York hospital were perplexed by the frequency of mild anemia developing in their patients after admission to the unit.

They postulated that this unexplained anemia might be the result of blood testing and designed a clinical study [1] to test their hypothesis. This included the first attempt to formally assess blood loss due to laboratory testing, revealing a mean daily blood loss of 54 ± 17 mL among their study population of 93 CCU patients.

In the mid-1980s, Smoller and Kruksall [2] demonstrated the greater blood loss due to laboratory testing among the critically ill compared with other hospitalized patients.

They retrospectively quantified blood drawn from 100 patients (50 ward patients and 50 intensive care patients) during admission to a Boston hospital and discovered that blood was sampled on average 1.1 times per day from ward patients but 3.4 times per day from intensive care patients. The mean daily blood loss was 12.4 mL for ward patients compared with 41.5 mL for intensive care patients.

During their hospital stay ward patients lost a mean total of 175 mL as a result of blood testing; the mean total loss for intensive care patients was 762 mL. For 10 of 50 (20 %) intensive care patients total blood loss exceeded 1000 mL.

More recently a prospective blood sampling study [3] of 1136 patients being cared for in 145 intensive care units across Europe revealed that the mean (SD) number of blood samples taken per day was 4.6 (3.2) and the mean (SD) total volume of blood sampled per day was 41.1 (39.7) mL.

Clearly, great variability was evident but a minority of patients suffered daily losses in excess of 100 mL.

Wisser *et al* [4] found that in an unselected in-patient population of 2654 at a single German hospital, 95 % of patients suffered total blood loss during their hospital stay of <200 mL, which they suggest is clinically insignificant.

The remaining 5 % (all intensive care patients) had total losses of greater than 200 mL and 0.7 % had losses in excess of 600 mL during their stay in intensive care.

Blood gas analysis is the most frequently requested blood test in intensive care, accounting for up to 40 % of blood loss due to diagnostic testing [5].

A UK study [6] revealed that intensive care patients had blood drawn for blood gases on average 8 times/day, and blood gas analysis alone accounted for a median daily blood loss of 45 mL.

## Clinical impact of phlebotomy in adults

To put the blood losses being discussed here in context, it is useful to keep in mind the total blood volume (70 mL/kg body weight). Thus an adult (weighing approximately 70 kg) has a total blood volume close to 5 liters.

Blood cells have a limited life (red cells 120 days), so that there is constant bone marrow production with around 1 % of blood volume (50 mL) replaced daily.

For the vast majority of hospitalized patients, the blood loss associated with laboratory testing, usually no more than 5-10 mL at any one time, represents just 0.1-0.2 % of total blood volume and is not sufficient to have clinical effect [4].

However, that is not necessarily the case for critically ill patients, who require more intensive monitoring. For these patients, in whom blood may be sampled up to 24 times a day [9], the studies outlined above suggest that the loss might be as high as 100 mL/day, equivalent to a 2 % reduction in blood volume.

Clearly, the length of stay in intensive care, severity and type of illness, plus local protocols for blood testing all have impact on the extent of blood loss due to laboratory testing for particular patients, but for all there is a potential risk of iron-deficiency anemia and consequent reduced oxygen delivery to tissues.

One mL of blood contains 0.5 mg iron; thus phlebotomy of 50 mL of blood represents a loss of 25 mg iron. A normal diet contains 10-15 mg/day of which 10-30 % is absorbed [7].

Even with maximum absorption, when 4.5 mg/day might be recovered from diet, daily phlebotomy of just 15 mL of blood (7.5 mg iron loss) inevitably leads to a negative iron balance within a few days.

The body has considerable iron reserves in storage (approximately 1000 mg for healthy adults) and anemia will not develop until these are exhausted.

However, it is clear that iron stores can be severely depleted by daily phlebotomy over a prolonged period; those with reduced iron stores on admission to intensive care being at greater than normal risk of phlebotomy-associated anemia.

Anemia is diagnosed when hemoglobin concentration falls below 13.5 g/dL (135 g/L) in males and below 11.5 g/dL (115 g/L) in females. Thavendiranathan *et al* [8] examined the effect of diagnostic phlebotomy on hemoglobin concentration among 380 patients hospitalized for, on average, 5.6 days.

They showed that for every 1 mL of blood removed for diagnostic testing, the mean (SD) decrease in hemoglobin was 0.07 g/dL (0.001). Thus a single draw of 50 mL of blood would be expected to reduce hemoglobin by 0.35 g/dL, and a stay in intensive care of 10 days during which 30 mL of blood were sampled daily would result in a fall in hemoglobin concentration of the order of 2 g/dL (20 g/L).

The particular vulnerability of intensive care patients for development of anemia is due not only to blood loss from diagnostic phlebotomy but also to the underlying critical condition that forced their admission, along with the associated complications that commonly occur during critically illness.

The most common causes of anemia in the critically ill, other than diagnostic blood loss, include: blood loss due to trauma, surgery or occult (e.g. gastrointestinal) bleeding, sepsis, disseminated intravascular coagulation and reduced bone-marrow red-cell production (blunted erythropoietic response).

All this means that anemia is a common feature of critical illness developing in 90 % of patients by the third day following admission to intensive care [9]. For around a half of these patients, anemia is of sufficient severity (<9 g/dL) to warrant red-cell transfusion [10].

It is highly unlikely that blood loss associated with blood testing would, of itself, result in anemia of this severity, but several studies have shown that it is a significant contributory factor towards the need for transfusion among the critically ill.

Von Ahsen *et al* [11] determined that blood sampling accounted for 17 % of the blood loss among 96 patients being cared for in intensive care, whilst Corwin *et al* [12] reveal that around 50 % of the variation in the amount of red cells transfused to intensive care patients can be accounted for by blood sampling.

Chant *et al* [13] conclude from a study of phlebotomy and the need for transfusion among 155 long-stay intensive care patients that *"small decreases in phlebotomy volume are associated with significantly reduced transfusion requirement"*.

## Clinical impact of phlebotomy for premature neonates

Among the many adjustments that occur during the first few weeks of life, as babies move from a supported uterine environment to physiological independence, is a gradual fall in hemoglobin concentration from around 17 g/dL at birth to 11 g/dL by 8 weeks of age.

This quite normal physiological reduction in hemoglobin is more rapid and severe in premature babies and leads to what has been called anemia of prematurity, in which hemoglobin may dip as low as 7 mg/dL. This predisposition to anemia among premature infants can be exacerbated by iatrogenic blood loss.

The impact of blood loss due to laboratory testing is greatest for the most premature neonates with very low birth weight (<1500 g), who all require many weeks of intensive monitoring and care.

This is a patient population for which the need for frequent blood testing is great, but circulating blood volume is small. Volume of blood per kg bodyweight is higher for neonates than it is for adults, but assuming a blood volume of 80-90 mL/kg these very small and frail infants have a total blood volume that may be as low as 50 mL, in which case sampling just 1 mL of blood reduces blood volume by 2 %.

Widness [14] observes that daily phlebotomy loss of 4-5 % of blood volume during the weeks immediately after delivery is not uncommon in this group.

Formal studies [15-17] suggest a weekly loss due to phlebotomy of the order of 10-25 mL/kg among premature neonates with a birth weight less than 1500 g. This represents a reduction in total blood volume of 10-30 % that inevitably contributes to the severity of anemia.

Close to 70 % of very-low-birth-weight babies require one or more red-cell transfusions during the first few weeks of life, and there is general consensus that a major cause of the need for transfusion is blood loss due to phlebotomy.

This view is based in part on studies [17, 18] that have demonstrated a very close correlation between volume of blood transfused and volume of blood removed for testing.

## Reducing blood loss due to laboratory testing

Iatrogenic anemia is a modifiable risk factor for prescription of red-cell transfusion. Minimizing patient exposure to the risks of transfusion is a clinical imperative that has highlighted the need for strategies to minimize diagnostic blood loss in the critical care setting.

Several approaches have proven useful, demonstrating that nurses, phlebotomists, clinicians, laboratory staff and manufacturers of laboratory equipment all have a contribution to make.

## Avoid unnecessary testing

There is evidence to suggest that laboratory testing in the intensive care unit is excessive; tests may be ordered as a matter of routine rather than necessity [19]. The adoption of written evidence-based guidelines for laboratory testing can have a significant effect in reducing the number of tests requested and ensuring that those tests requested are really appropriate [20, 21].

Merely providing physicians with information about the cost of testing can help to reduce unnecessary testing according to the results of one French study [22] and careful monitoring of the accumulative volume of blood sampled from each patient can modify test requesting.

## Oversampling

It is of course important to ensure, so far as is possible, that no more blood is sampled than is actually required for the analytical process.

The extent of oversampling has been highlighted by Marquis *et al* [22], who studied blood-sampling practice in an adult intensive care unit over a 10-week period. They discovered that the volume of blood sampled was between 4 and 20 times higher than the actual volume used for analysis.

Similarly, an audit of blood sampling practice at 140 US hospitals [23] revealed that laboratories collect a median of 2.76 mL (i.e. 8.5 times) more than is actually required for full blood count, and a median of 1.75 mL (i.e. 12 times) more than is actually required for electrolyte profile.

The authors of this audit conclude that *"most laboratories can decrease collection volumes without compromising the ability of the laboratory to report a reliable and timely result"*.

A simple partial solution to the problem of oversampling in the adult intensive care unit is to use pediatric blood-collection tubes. Smoller *et al* [24] report a 47 % reduction in iatrogenic blood loss following the switch from regular blood-collection tubes to pediatric tubes.

## Reducing discarded blood obtained via indwelling catheters

In a critical care setting blood is frequently sampled via an indwelling catheter, most often sited at the radial artery in adults and the umbilical artery in neonates.

The patency of these catheters is maintained by a heparin

or saline flush solution. It is essential for accurate results that blood is uncontaminated with flush solution and to this end a volume of blood must be discarded (to clear the line of all traces of flush solution) prior to blood collection.

A minimum discard volume of the order of 2 mL is generally recommended but the actual volume depends on local practice and has been reported to be as high as 10 mL [5]. A number of devices are available to conserve this discarded blood and safely return it to the patient after the uncontaminated sample has been collected [25].

A randomized controlled trial of one such device on a study population of 160 intensive care patients [26] revealed that median total blood loss due to diagnostic testing was 133 (range 7-1227) mL for 80 patients randomly assigned to have blood sampled conventionally via an arterial line, compared with just 63 (range 0-787) mL for the remaining 80 patients who were assigned to have blood sampled via arterial line to which the conservation device was connected.

In this study the blood-conserving device reduced total blood loss due to testing by close to 50 %.

## Point-of-care testing

Although of emerging significance, point-of-care testing (POCT) has the greatest potential of all the strategies discussed here to reduce iatrogenic anemia among the critically ill. Nearly all of the common blood tests used to monitor critically ill patients can now be performed at the point of care.

For well over two decades, blood gas analysis has been conducted within intensive care units at the point of care. Modern blood gas analyzers now have the capacity to measure not only blood gas parameters (pH, $pCO_2$ and $pO_2$) but also an ever-increasing number of chemical and hematological parameters that have hitherto been the sole preserve of the central laboratory.

Moreover, all these measurements can be made using a single, small (100-150 µL) whole-blood sample. The principal advantage of point-of-care testing in a critical care setting is decreased turnaround time, but a secondary advantage is decreased blood loss for diagnostic testing.

A recent study [26] provides evidence of this beneficial effect of POCT. The study was conceived when a POCT analyzer was installed in a Californian neonatal intensive care unit. It provided clinicians with the opportunity to assess the impact of this new technology on the frequency of red-cell transfusions.

The newly installed POCT analyzer measured blood gases, hemoglobin, hematocrit, sodium, potassium and ionised calcium simultaneously using just 100 µL of whole blood. Prior to the introduction of POCT to this unit, all these tests were performed in the laboratory and required a minimum blood volume of 1000 µL.

The study focused on all 80 very-low-birth-weight (<1000 g) babies admitted to the unit during 2 separate years, the first before and the second after installation of the POCT analyzer. The medical records relating to the first 2 weeks of life for each of these babies were retrospectively reviewed.

Analysis revealed that despite the fact that there was no significant difference between the two groups in terms of the number of tests performed, the mean number of red-cell transfusions in the first 2 weeks of life was 5.7 ± 3.74 in the pre-POCT group compared with 3.1 ± 2.07 in the post-POCT group, a reduction of 46 %. A similar-sized reduction between the two groups was noted for the mean volume of red cells transfused.

## Summary

For the vast majority of hospitalized patients, the blood loss associated with diagnostic testing is of little or no clinical significance. That is not necessarily the case for two patient groups: critically ill adults/children and very premature babies.

Both groups are predisposed to anemia, and the relatively large blood loss associated with diagnostic

testing can increase the severity of that anemia such that transfusion of red cells may be necessary.

To minimize exposure of these already very sick patients to the additional risks associated with blood transfusion, it is important that the inevitable blood loss associated with laboratory testing is kept to an absolute minimum.

A number of strategies have proven useful in this regard. Although still in its infancy, point-of-care testing will probably prove the most effective of these.

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