SPECIAL REPORT

Handling Hemolytic Blood Samples from High-Risk Clinical Areas: A Call to Action

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Background: Spectrophotometric testing to detect sample hemolysis is available from central laboratory chemistry analyzers. While the cause and preventative measures are known, hemolysis continues to be a common preanalytical error, especially for specimens collected from the emergency department (ED) and intensive care units (ICUs) where point-of-care analyzers are commonly used for whole blood electrolyte testing. Recently, these analyzers have employed technology to detect hemolysis directly on whole blood samples.

Methods: Experienced laboratorians and physicians from the clinical laboratory, ED, adult and neonatal ICUs provide a summary of the medical importance of in vitro hemolysis. Causes for in vivo hemolysis are summarized as it is indistinguishable from in vitro hemolysis from routine laboratory analysis. The detection of hemolysis by clinical laboratories is discussed from the American and European perspectives.

Results: In vivo hemolysis can occur due to genetic abnormalities, hemoglobinopathies that cause red cell lysis, and mechanical circulatory support. There are many causes of in vitro hemolysis. Patients in the ED and ICU are particularly vulnerable to erroneous laboratory data such as potassium. Incorrectly treated patients can lead to significant medical consequences. Within the clinical laboratory, there are recommendations made by accrediting bodies, but none are mandatory, and the implementation of the hemolysis index testing is not universal.

Conclusions: Recommendations have been authored regarding the need for education for prevention, performance of hemolysis detection testing, defining levels of hemolysis reporting, periodic monitoring of hemolysis detection performance, and laboratory reporting practices for high and normal potassium test results.

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IMPACT STATEMENT

In vitro hemolysis occurs when there is turnover of red blood cells in a blood sample and can lead to erroneous laboratory tests such as for potassium. The most impactful areas are the emergency department and intensive care unit. Clinical laboratories must actively test for hemolysis and other interferences in serum, plasma, or blood samples and have a protocol for addressing these issues.

INTRODUCTION

The three phases of testing for clinical laboratory tests are the preanalytical, analytical, and post-analytical. Characterizing the quality of samples in the preanalytical phase of testing has been recognized as the most common source of error (1). Within this category, testing of hemolyzed samples may have the most medical significance. By definition, hemolysis is the rupture of red blood cells and release of their contents. This can be due to an in vivo, physiologic hemolysis from an underlying condition such as autoimmune hemolytic anemia or the use of extracorporeal membrane oxygenation (ECMO). In vitro is the lysis of red blood cells due to phlebotomy, specimen handling, or transport that artificially impacts laboratory results (Fig. 1) (2–5). Hemolysis is the most common cause of specimen rejection in the total testing process, accounting for 18%–96% of rejected specimens (2). While hemolysis rates vary between hospital locations (Fig. 2) (3), it has been most frequently documented in the emergency department (ED). There, hemolysis rates are as high as 25%–30% (4), with specimen rejection rates exceeding 4% (5). Importantly, hemolysis can lead to misinterpretation of laboratory values that can have important clinical ramifications. Moreover, they can result in a decision to re-draw and retest, delaying turnaround time and prolonging the patient's length of stay (6).

To date, assessment of hemolysis is most often performed using central clinical chemistry laboratory analyzers that make photometric measurements and determine the presence of hemolysis, high bilirubin and lipid levels (HIL) in serum or plasma samples. The presence of these interferents are reported as a laboratory use only result, and enables a determination of test accuracy. The mechanism of interference may be spectrophotometric, proteolytic due to enzyme release from red blood cells, or due to release of intracellular contents that exceed the true concentration in the serum or plasma. Alternatively, some laboratories may use visual inspection of a specimen to assess for hemolysis; a practice that is considered inferior to automated hemolysis detection due to inaccuracy of color detection (7). Many analytes are impacted by hemolysis, but potassium results are particularly affected due to the release of the intracellular cation upon red cell rupture.

While numerous methods are available for the assessment of hemolysis in plasma, historically, there have been limited methods available for its detection in whole blood. Measurement of potassium and other electrolytes in this matrix have been available for many years using blood gas analyses. This approach, especially when point-of-care (POC) analyzers are used, can produce faster results than can be obtained from the central laboratory, as the latter requires sample centrifugation and delivery from the collection site to the central laboratory. The disadvantage is that most blood gas analyzers are unable to detect the presence of interferences such as hemoglobin. In the absence of hemolysis testing, results for potassium analysis are presumed to be correct and

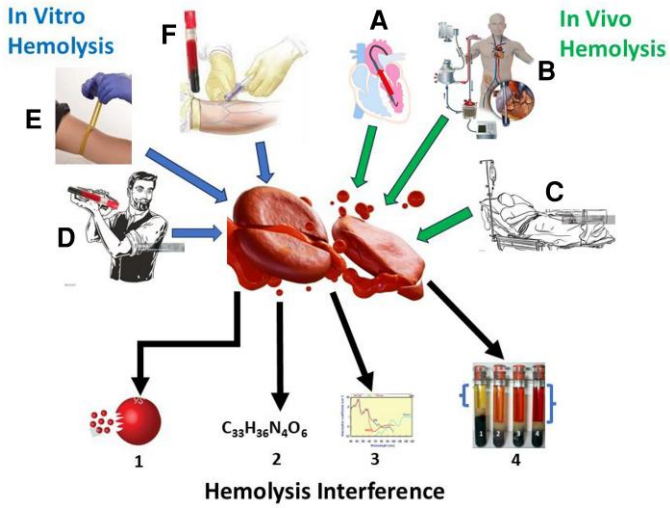

Fig. 1. Hemolysis causes and consequences.

In vivo hemolysis causes

(A) Ventricular assist devices
(B) Extracorporeal membrane oxygenation (ECMO) treatment
(C) Medications: dapsone, cephalosporins, arsenic; illnesses: sickle cell anemia, hemolytic anemia

Interference mechanisms

1. **Intracellular release**
   - **Potassium, lactate dehydrogenase, aspartate, alanine aminotransferase, magnesium, and phosphorus all have higher red blood cell intracellular concentrations vs serum/plasma**
   - **Drugs/toxins cause hemolysis: dapsone, cephalosporins, arsenic**
2. **Measurement chemical interference**
   - **Hemoglobin's impact on bilirubin measurement**
   - **Overestimation of creatine kinase due to red blood cell release of adenylate kinase**
3. **Spectrophotometric interference**
   - **Oxyhemoglobin absorption from 320 to 450 nm, peak 415 nm**
   - **Deoxyhemoglobin absorption from 540 to 589 nm**
   - **Lipase, albumin, and gamma glutamyltransferase measurements overestimated**
   - **alkaline phosphatase will be underestimated when hemoglobin is degraded in alkaline medium**
4. **Dilutional effect interference by**
   - **Classic examples: Na^+, Cl^- and glucose; Na^+ changes are clinically significant**
   - **Analytes with lower red blood cells intracellular concentrations are impacted by dilutional effect to serum/plasma**

In vitro hemolysis causes

(D) Shaking tubes or pneumatic tube transport
(E) Extended tourniquet time
(F) Phlebotomy syringe use, small (large-gauge) needle use

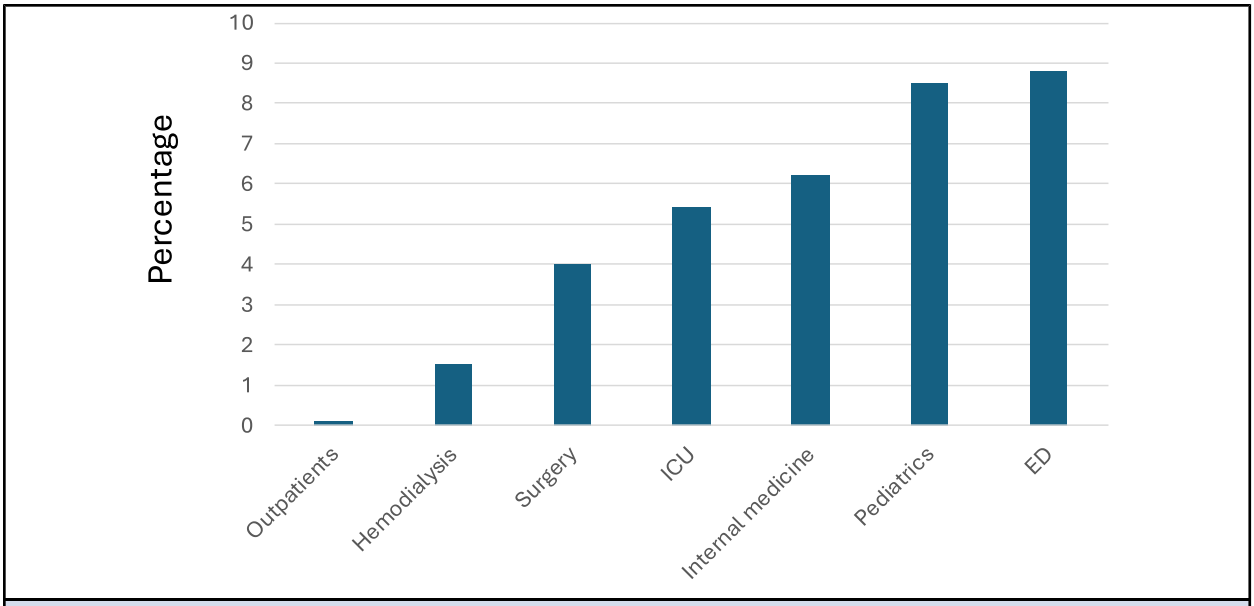

Fig. 2. Prevalence of hemolyzed specimens according to the healthcare setting. Adapted and used with permission of Walter De Gruyter GmbH, from "Survey on the prevalence of hemolytic specimens in an academic hospital according to the collection facility: opportunities for quality improvement," G. Lippi, G.L. Salvagno, E.J. Favaloro, G.C. Guidi, *Clinical Chemistry and Laboratory Medicine*, 47(5), 2009 (3); permission conveyed through Copyright Clearance Center, Inc.

can lead to inappropriate medical decisions by medical providers. Some laboratories may centrifuge specimens after testing the whole blood to assess for hemolysis in plasma. However, this practice is labor-intensive, offsets some of the time gained by testing whole blood, and is not feasible at the POC.

In 2016, the Australasian Association of Clinical Biochemists (AACB) and the Royal College of Pathologists of Australia (RCPA) published a series of consensus statements and commentary regarding the management and reporting of hemolyzed specimens (8). The general concepts presented in those consensus statements have not changed, and the statements contained herein are similar to those previously rendered. However, since the publication of that document nearly a decade ago, it is now possible to detect hemolysis in whole blood specimens (9). Given the overall importance of specimen hemolysis, recognized or otherwise, the authors of this document felt it appropriate to revisit this issue. The AACB/RCPA statements were written from a clinical laboratory perspective. Unfortunately, the scope of the specimen hemolysis problem has likely not been lessened (1).

In this document, we present the importance of hemolysis detection from a clinical perspective, seeking narratives from physicians with responsibilities for treating patients with in vivo hemolysis, and those doctors who practice in the ED and adult and neonatal intensive care units (ICUs) and must make medical decisions regarding in vitro hemolysis. There are other medical areas that utilize whole blood electrolyte testing, such as the operating room, urgent care settings, and emergency transportation vehicles. There are also specialized settings such as the cardiac catheterization laboratory, centers that use ECMO, ventricular assist devices (VADs), and other medical applications that have been associated with a higher than average risk for producing a hemolytic specimen.

We describe the experience in the United States and Europe regarding current hemolysis detection laboratory practices. A series of recommendations are presented where agreement has been achieved by this report's multidisciplinary and multi-national experts.

THE MEDICAL ISSUES OF IN VIVO HEMOLYSIS

This document focuses on in vitro hemolysis, a significant cause of preanalytical laboratory error. However, intravascular and extravascular hemolysis is also a reason for the presence of free hemoglobin in a collected blood sample and must be considered. In vivo, hemolysis can be caused by multiple factors, including red blood cell (RBC) genetic conditions that cause RBC abnormalities and lysis, including hemoglobinopathies such as sickle cell disease or spherocytosis (10). There are multiple acquired conditions that can produce in vivo hemolysis including patients receiving mechanical circulatory support (cardiopulmonary bypass, ECMO, and VADs including Impella and intraortic balloon pumps), prosthetic heart valves, some drugs (11), and acute infections associated with disseminated intravascular coagulopathy (DIC) (12). Patients with hemolysis due to multiple causes, including hemoglobinopathies, are at increased risk of thromboembolism (13).

Clinical manifestations vary depending on whether acute or chronic hemolysis occurs. Commonly, in-hospital patients are often critically ill, especially in the ICU, and are managed with lower hemoglobin and hematocrit thresholds compared to healthy outpatients. Inpatients receiving mechanical circulatory support are often evaluated daily for hemolysis by laboratory measurements of hemoglobin and hematocrit levels, lactate dehydrogenase (LDH), haptoglobin levels, and indirect bilirubin (14).

Clinical management of in vivo hemolysis involves initially removing and/or treating the underlying cause, initial RBC transfusions, giving vitamins, and erythropoietic agents (14). The procoagulant effects of hemolysis are substantial and have important clinical implications. For example, anticoagulation is a critical component in mechanical circulatory support due to extracorporeal effects and the nonendothelial interface of blood with circuits (15).

There are no laboratory tests that can differentiate between in vivo and in vitro hemolysis. Therefore, when the laboratory reports its presence, the distinction between these two etiologies must be made on clinical grounds by the attending medical staff. The absence of use of mechanical circulatory support and normal clinical laboratory results for hemolysis indicators can be useful in ruling out an in vivo hemolysis etiology.

This section was written from the perspective of a critical care physician at an academic medical center in the United States with speciality in cardiothoracic surgery, cardiogenic shock, and mechanical circulatory support, with expertise in thrombosis and hemostasis.

MEDICAL IMPORTANCE OF HEMOLYSIS DETECTION: EMERGENCY DEPARTMENT

In addressing hemolysis, the contemporary ED has one of the largest exposure risks for inpatients. This is a result of a complex of specific challenges. The sheer volume of patients seen makes the ED a high-risk area for hemolysis. Data from the Ambulatory and Hospital Care Statistics Branch show that an estimated 130 million patients are seen in US EDs annually, of whom as many as 50% may have blood drawn for laboratory testing (16). This equates to as many as 65 million laboratory draws that may potentially have some degree of hemolysis. When blood collections are needed, invariably, the metabolic panel is ordered. Of this panel, potassium plays a particularly

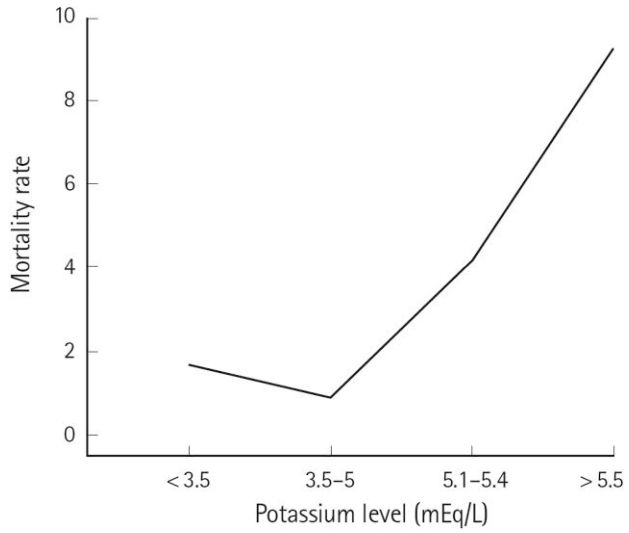

Fig. 3. Mortality of potassium concentrations among emergency department patients. Reprinted from Singer et al., https://doi.org/10.15441/ceem.16.194 (18) under https://creativecommons.org/licenses/by-nc/4.0/.

central role in diagnostic processes. ED studies have shown that hypokalemia (<3.5 mmol/L) is associated with a 2-fold increase in mortality, while mild (5.1 to 5.4 mmol/L), and severe hyperkalemia (>5.5 mmol/L) are associated with a 4.0-, and 9.0-fold increase in mortality, respectively (17) (Fig. 3).

Within the ED, it is common to have nonlaboratory-trained staff perform phlebotomy, and they are more likely to produce a hemolyzed specimen. This is further exacerbated due to high job turnover within the ED environment, such that inadequate training on how to avoid hemolysis (18) is common and ultimately results in excessively high ED hemolysis rates (4). The ED has a critical need for rapid testing, which is commonly addressed by the use of whole blood POC testing (19). The inability to detect hemolysis in whole blood testing systems and, therefore, without the ability to evaluate or report its presence magnifies this problem. These confluences of factors ultimately result in an area of care where hemolysis of laboratory specimens is common (4), dangerous (20), expensive (17), and may go undetected (21).

This section was written from the perspective of an emergency physician in an academic medical center in the United States who conducts research and performs clinical trials in emergency medicine, cardiology, and laboratory medicine.

MEDICAL IMPORTANCE OF HEMOLYSIS DETECTION: INTENSIVE CARE UNIT

Critical care medicine involves precise, reliable, accurate, appropriate, and timely decision-making. Early recognition of medical complications or life-threatening conditions is crucial to improving clinical outcome and reducing mortality. With laboratory testing, a provider can intervene before a patient deteriorates clinically. Unfortunately, laboratory tests are not without limitations. Serum rather than plasma potassium can be affected by platelet count and white blood cells (22). Moreover, vacuum tubes, tourniquet usage, pneumatic tube transport, and extended incubation can also lead to cell lysis and pseudohyperkalemia (falsely elevated) (23). In critically ill patients, these effects can severely alter

a clinician's decision pattern and result in clinical errors. While repeat testing is pending, most patients with pseudohyperkalemia will undergo a number of diagnostic and treatment strategies. In nearly all cases of hyperkalemia, electrocardiogram (ECG) testing is used to assess for peaked T-waves, widened QRS, first-degree AV blocks, bradycardia, ST depressions, U-waves, or other arrhythmias. In addition to ECG costs, the time needed for a provider to interpret scans is time taken away from other patient needs.

Critically ill patients often cannot afford additional medical, surgical, or therapeutic complications. ICU providers routinely encounter life-threatening cardiac electrophysiological disorders caused by hyperkalemia. Therefore, treatment for the suspected potassium derangement is often given simultaneously while potassium retesting for suspected hemolysis is performed. There are several therapeutic interventions that would be unnecessarily employed. Simultaneous administration of insulin and glucose can have dysglycemic complications. Approximately 17% of patients who received insulin–dextrose therapy for hyperkalemia developed clinically significant hypoglycemia (24). High glucose doses in ICU patients can further precipitate organ and vascular dysfunction (25). Therefore, critically ill patients, especially those with renal failure, will then typically require follow-up hourly glucose monitoring.

The use of β-2 agonists can be administered via nebublization or intravenous administration. In cases of pseudohyperkalemia, this can result in unnecessary cardiovascular excitability (tachycardia and vasoconstriction) and arrhythmic disorders due to sympatho-adrenal activation. Additionally, hyperglycemia and lactic acidosis can arise. Type-B lactic acidosis can result in further unnecessary diagnostic and treatment interventions, i.e., CT-imaging and intravenous fluids.

Loop diuretics are sometimes prescribed to increase potassium urinary excretion, especially in symptomatic fluid-overloaded patients. When given unnecessarily, this can have detrimental, unpredictable natriuretic and kaliuretic effects, especially in those with renal or heart failure. It can also lead to avoidable hyponatremia, metabolic alkalosis, hypophosphatemia, and hypomagnesemia. Sodium polystyrene sulfonate facilitates gastrointestinal potassium excretion. However, life-threatening intestinal perforation can arise (26). Patiromer is a potassium-binding polymer and when used can result in needless gastrointestinal upset and hypomagnesemia (27). Hypertonic sodium bicarbonate infusions are routinely prescribed in patients with acidosis, renal failure, or hypovolemia to achieve volume resuscitation, cardiac membrane stabilization, and serum potassium lowering. In patients with pseudohyperkalemia, this can result in a fluid overload state and severe life-threatening metabolic alkalosis. In some cases, especially in patients with renal failure, renal replacement therapy or peritoneal dialysis is initiated to correct the electrolyte derangement. This can result in rapid fluid shifts, electrolyte changes, and bleeding due to anticoagulation (28).

A rapid detection of hemolysis can help obviate unnecessary hypokalemic treatments and avert critical cardiac events and sudden death (29). Finally, ICU providers often spend a considerable amount of time endeavoring to find the source of the hyperkalemia. This time spent unnecessarily on pseudohyperkalemia takes time away from critically ill patients with true complications.

This section was written from the perspective of an intensive care physician in an academic medical center in the United States, with responsibilities in medical and surgical intensive care units and research in infectious diseases.

HEMOLYSIS IN BLOOD SAMPLINGS FROM THE NEONATAL PATIENT

Whole blood POC testing is commonly used in the neonatal ICU (NICU) due to important

advantages such as the quick turnaround time and blood saving in very small patients, mostly in neonates that exhibit frequent blood gases and electrolytes variations. Many clinical situations require close control of electrolyte concentrations during the first few days after delivery. This is especially true in premature infants where hyperkalemia is frequent due to the physiologic postnatal hemolysis that occurs to reduce in-uterus excessive hemoglobin concentration, and because of immature renal function.

Whole blood potassium measurements performed in the NICU are often misinterpreted because of unrecognized hemolysis. It has been reported that approximately 20% of plasma potassium specimens in children less than 2 years of age are hemolyzed, with rates near 50% in the neonatal nursery setting (30). This can result in up to 4 mmol/L overestimation of circulating potassium concentration. This can go up to 70% in some NICU reports (31), mostly in the more immature infants where technical problems related to the collection of samples, milking, and ischemia are more frequent.

Blood collections obtained via syringes are subject to repeated shear forces and are prone to produce hemolysis. Moreover, for immature infants in particular, the site of heel stick bleeding is often massaged or "milked" to obtain adequate blood volume for testing. This leads to physical disruption of erythrocytes and leakage of intracellular potassium into the humoral compartment of the blood sample. The result is an overestimation of circulating potassium of approximately 5 mmol/L for every gram per deciliter increase in cell-free hemoglobin.

Within the NICU, due to the patients' characteristics and difficulties in obtaining a high-quality blood sample, potassium concentrations may be frequently falsely increased or may be falsely normal (pseudoeukalemia) hypokalemia that can go unrecognized by caregivers (32). Severe hyperkalemia can be underdiagnosed until the time that severe symptoms appear. Due to the low circulating blood volumes found in neonates, repeat phlebotomy in an attempt to produce a nonhemolyzed sample may be difficult to justify. Due to their high risk of hemolysis, there is a high likelihood that in vitro hemolysis will recur.

To prevent this risk of medical errors related to misinterpretation of potassium in whole blood, new instrumentation capable of identifying the presence of interfering substances in whole blood samples such as hemolysis are especially needed in the neonatal and pediatric ICU (33). The rationale for this detection includes the need for potassium supplementation or depletion, which can produce a significant deleterious effect if such decisions are made from an erroneous potassium measurement. The suspicion of hemolysis in whole blood specimens comes with short-term consequences including specimen re-collection, inappropriate treatment, and/or delays in treatment. Retesting comes with risks, including delays in treatment, iatrogenic anemia, the need for transfusion, and discomfort to the neonate. The pain is associated not only with impaired neurodevelopment, but also mood and behavioral disorders. Therefore, recognizing hemolysis is key in the NICU as this will improve diagnosis and therapy, preventing side effects due to a delay in therapy or inappropriate therapy or testing, and preserving precious circulating blood volume by not performing repeat blood collection.

This section was written from the perspective of a neonatologist at an academic medical center in Spain with expertise in neonatal respiratory physiology, immature lung damage prevention, neonatal cardiovascular support, and personalized nutrition.

CURRENT CENTRAL LABORATORY AND POINT-OF-CARE TESTING PRACTICES: UNITED STATES

In the central laboratory, practices for assessing hemolysis vary based on the specimen type (i.e., Vacutainer vs syringe) and on the availability of

Table 1. Approaches for hemolysis indicators from selected chemistry analyzer manufacturers.

Manufacturer (analyzer)	K^+ hemolysis claim	Criterion ±10%	Reporting manner	Wavelength, nm
Roche (cobas 8000)	H-index ≤20	0.1 mmol/L	Numeric	570, 600
Abbott (Alinity c)	Free hemoglobin <0.125 g/dL	±10%	Numeric	500, 524
Siemens (Atellica)	Flag 1, hemolysis index: 11–130	NA	Index, 0–6	571, 596
Beckman Counter (DxC)	Free hemoglobin <0.070 g/dL	<0.25 mEq/L	N (<50), +(50–99) to +++++ (>500)	410/480, 571
QuidelOrtho Vitros	"Do not use hemolyzed specimens"	NA	Numeric, 1-	Spectral Scan 400-800
Mindray 800M	"Avoid hemolyzed samples"	NA	Index, +, ++, etc.	570, 660

Abbreviation: NA, not applicable.

automated systems for detecting hemolysis. Automated chemistry analyzers use spectrophotometry to assess for the presence of free hemoglobin and report a laboratory use only result known as the "hemolysis index" (HI). This allows for a rapid and highly reproducible measurement of the amount of free hemoglobin. The Clinical and Laboratories Standards Institute (CLSI) Document C56 addresses best practices for assessing hemolysis and suggests that laboratories use automated determination of the HI and verify manufacturer claims for hemolysis, particularly for assays highly prone to hemolysis interference (34). Using this approach, some laboratories have used the HI to extend the measuring ranges on some analytes based on concentration (35). Further, some laboratories have used the HI (and by extension free hemoglobin) to correct for changes in intracellular analytes such as potassium in hemolyzed specimens (36). The CLSI recommends against the use of the HI for correcting an analyte value (34). However, some laboratories use tiered hemolysis thresholds in a comment-based approach report for potassium and other analytes from mildly and moderately hemolyzed specimens (37).

An important limitation of automated hemolysis assessment is the variability between automated systems and the differences in implementation of the HI between laboratories. While the HI is useful for approximating the amount of plasma free hemoglobin, the relationship is imperfect. One recent study found a correlation of 0.81 between the HI and plasma free hemoglobin (as measured by a pseudoperoxidase method) when the free hemoglobin was <25 mg/dL. Similarly, there is a lack of consistency between chemistry analyzer vendors and how hemolysis is reported, with some using a continuous numeric and others using alpha characters such as a "+" or a scale of 1–6 (Table 1). There is also variability in the wavelengths used to assess for hemolysis (Table 1). While comparable, there is an imperfect relationship between the HI results across platforms, and the HI has not been harmonized (38). Furthermore, manufacturers have varying claims for hemolysis for specific analytes. Claims for some vendors on current models of chemistry analyzers for potassium are shown in Table 1. Moreover, the methods used by vendors for analytes may differ, and thus have a varying impact from hemolysis (39). There are limited data comparing practices for hemolysis assessment in US-based hospitals with some laboratories validating their own hemolysis thresholds for a given analyte (35). Other approaches have been validation and implementation of tiered hemolysis thresholds (36). Most laboratories implement hemolysis thresholds using autoverification rules;

however visual checks may still be used in some circumstances and are supported on the preanalytic line of some vendors (40). Finally, spectrophotometric interference may be diluted in some circumstances, but there is no literature addressing varying practices between laboratories.

Despite the availability of automated methods for hemolysis detection on chemistry analyzers, there are limited requirements or recommendations from accrediting bodies or in federal standards. The College of American Pathologists (CAP) requires that accredited laboratories have criteria for the rejection of specimens that do not meet predefined criteria for quality but allow each laboratory to define their own methods and standards for identifying/defining hemolysis (COM.06300). Furthermore, CAP also requires that laboratories provide feedback to collectors (phlebotomists) regarding specimen quality, but do not define how to provide feedback nor the elements that relate to specimen quality, including hemolysis. Similarly, other accrediting agencies such as the Joint Commission and The Commission on Office Laboratory Accreditation (COLA) make no statements regarding evaluation of specimen quality with regards to hemolysis. The Clinical Laboratory Improvements Amendments of 1988 (CLIA) regulations, which govern laboratory testing in the United States, have no requirement for specimen quality regarding hemolysis. Interestingly, the U.S. Food and Drug Administration (FDA), as part of a CLIA waiver requirement state that any manipulation of a specimen, including the need to evaluate for hemolysis by an operator, is a limitation for a test to be considered "simple" (41). Given the variation and lack of regulatory requirement, it is perhaps unsurprising that there is no common definition of a "hemolyzed specimen" within the United States.

Whole blood specimens such as blood gas syringes used at both POC and in the laboratory setting provide additional challenges for hemolysis detection. The vast majority of sample-to-answer instruments lack automated detection systems for the assessment of hemolysis. If instruments are available, some laboratories will centrifuge whole blood specimens after testing and assess the degree of hemolysis relative to a hemolysis chart (8). A limitation of visual interpretation is that it has poor agreement with the concentration of free hemoglobin in a specimen, resulting in interrater disagreement and poor sensitivity for hemolysis. Centrifugation and visual interpretation will prolong turnaround time in whole blood testing. To this end, a limitation of the CLSI C56 document is that it does not make recommendations for handling and reporting of whole blood specimens when assessing for hemolysis (34). Some laboratories adopt policies in which specimens with abnormal results, such as elevated potassium, require specimens to be sent to the laboratory for further analysis. However, there is minimal data demonstrating compliance rates by nonlaboratory personnel to such a policy or the efficacy of such an approach. To this end, previous recommendations for managing hemolysis in clinical specimens have explicitly stated that POC testing lacks quality from published evidence (42).

This section was written from the perspective of a clinical chemist working at a large academic medical center in the United States.

CURRENT MANAGEMENT OF HEMOLYSIS DETECTION IN THE CLINICAL LABORATORY AND AT THE POINT-OF-CARE IN EUROPE

The current preanalytical practices in European clinical laboratories regarding detection and management of hemolyzed samples are highly heterogeneous and need improvement. In one study of 1347 participants from 37 European countries, 14% of all responders reported no monitoring for hemolysis, icterus, or lipemia (HIL) (43, 44). Even more strikingly, 80% of those laboratories

stated they were accredited or certified (44). Therefore, published international standards, e.g., ISO 15189 and those from the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group for Preanalytical Phase (WG-PRE) recommending HIL testing (45) were ignored.

According to the EFLM WG-PRE survey, the HIL index was mostly checked in routine clinical chemistry samples but less frequently for coagulation, therapeutic drug monitoring, or serology/infectious disease testing (44). Studies from the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC) showed that even mild hemolysis affected coagulation tests like activated partial thromboplastin time and d-dimer to a large extent, with a less pronounced effect for antithrombin and fibrinogen (46). Furthermore, certain immunoassays can also be impacted to a large extent by hemolysis (47).

The method of identifying hemolysis varied widely among the 1347 surveyed European laboratories. Measurement of the HIL index was performed either automatically by HIL indices (43% of laboratories), by visual inspection of samples (30%), or by a combination of both (43). Only 25% of laboratories using automated HIL-index measurement stated that they are using internal quality controls to check the quality of these measurements on a regular basis. Subsequently, hemolysis cutoff definitions like analyte-specific thresholds as well as protocols to either reject, report, or flag hemolytic samples were even more heterogeneous (44).

There are several publications by the EFLM WG-PRE to further address hemolysis detection as an important preanalytical key issue, like a call for more transparency and some practical recommendations for improving the harmonization of the automatic assessment of serum indices and their clinical usefulness, specifically the HI (48). Recommendations include how to manage local quality assurance of serum or plasma HIL indices and how to detect and manage hemolyzed samples in clinical chemistry testing (42). Simundic et al. conclude that given the high prevalence of hemolyzed blood samples and the great heterogeneity in how hemolysis is handled across different healthcare settings and countries, standardization and quality improvement processes aimed at combatting this important preanalytical problem are warranted (49).

Despite the fact that hemolysis is quite common in the ICU and ED and has a tremendous impact on critical POC tests like potassium, partial pressure of oxygen and carbon dioxide, or ionized calcium measured by blood gas analyzers (50), detection of hemolysis for POC testing ranges from neglected to predominantly nonexistent in Europe. There are some devices available for photometric hemolysis detection, like the Helge HemCheck that might be used at the POC (51), which measures free plasma hemoglobin. The disadvantages of such tests are that they require manual steps with significant hands-on time and do not give a quantitative result for free plasma hemoglobin or an HI, but only define the sample as positive or negative for hemolysis at a predefined cutoff value by the user. With the current challenges of nursing staff shortages and already critical workload for care providers in the ICU and ED (52), such devices are not suitable for a busy and strenuous POC testing environment. To overcome these obstacles and to improve patient care and safety, a built-in automated hemolysis detection system should be an integral part of any blood gas analyzer.

This section was written from the perspective of a specialist for laboratory medicine physician working in a clinical laboratory in Germany that serves 10 hospitals.

RECOMMENDATIONS

Recommendation Statement #1

As part of routine competency, the clinical laboratory should establish preanalytical educational programs for their internal staff, and for all

house staff members who collect patient samples, and in particular, staff who perform whole blood POC measurements. Important objectives of these programs include conveying how hemolytic samples are produced, best practices for blood collections, and the steps that can be taken to reduce the production of hemolytic samples.

Recommendation Statement #2

Using semiquantitative spectrophotometric techniques from clinical chemistry analyzers, the clinical laboratory should perform testing and when hemolysis is present, report indicators for serum, plasma, and whole blood (if possible) for samples. As there is currently no standard in the field for reporting this critical information, professional associations should work toward their development.

Recommendation Statement #3

Directors of clinical laboratories should consult with the pertinent local medical practice committees to determine the level of *mild* hemolysis that should trigger an alert to accompany the test result, and at what level of *significant* hemolysis should test results not be reported. Information provided by the relevant instrument manufacturers should also be reviewed. These limits should be defined on a test-by-test basis as hemolysis does not affect all clinical laboratory tests equally.

Recommendation Statement #4

As part of good laboratory practices, the clinical laboratory must routinely monitor the quality of hemolysis detection. As a preanalytical indicator of performance, laboratories should report an appropriate metric of hemolysis rate at regular intervals (e.g., quarterly) as a quality assurance indicator. This will enable the laboratory staff and all stakeholders to establish threshold standards and target areas of improvement for this important preanalytical interference. This will enable corrective actions to be taken and will improve the overall quality and safety of laboratory testing. Monitoring, establishment of performance indicators, and reporting of metrics should be routine practice in clinical areas where in vivo hemolysis is an issue, such as with use of ECMO and VADs.

Recommendation Statement #5

Users must be made aware of the risk when the hemolysis status is unknown, and testing with POC devices should be interpreted with caution unless concurrent testing for hemolysis is conducted. For all patients with hyperkalemia, the clinical laboratory should consider amending the report with an alert notating that results could be falsely high. The medical team should have an option to have the sample centrifuged and sent to the central laboratory for retesting to determine the presence of hemolysis. An alert could be made suggesting a recollection with the sample sent to the central laboratory.

Recommendation Statement #6

A whole blood sample from a patient with hypokalemia can produce a normal potassium result in the presence of hemolysis. Unless there is concurrent testing for hemolysis, it will not be possible for the laboratory to detect this situation, as it is not recommended to make any notes of the possibility of hypokalemia due to hemolysis, and it is entirely impractical to have all samples with normal potassium be sent to the clinical laboratory for results verification. In this situation, the medical team can contact the laboratory to conduct additional analyses when hypokalemia is suspected, e.g., from a patient's presenting symptoms, without any prompts from the laboratory.

Nonstandard Abbreviations: ED, emergency department; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; HIL, hemoglobin, icterus, lipema; POC, point-of-care; NICU, neonatal intensive care unit; HI, hemolysis index.

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