Reducing Analytic Laboratory Error to Improve Patient Safety and to Reduce Medical Costs

Wendy S. Sprague, DVM, PhD
Sprague Medical and Scientific Communications

ABSTRACT

Health care reform, which began in the late 1990s, energized the health care community to create a more patient centric health care system. In 2008, the CDC analyzed the effect of laboratory medicine on patient care and recommended quality improvements in laboratory medicine testing and reporting. Within this scope, total laboratory error has been stratified into three phases: pre-analytic, analytic, and post-analytic error. The main endogenous laboratory tests interferents include hemolysis, icterus, turbidity and viscosity, and they fall into the category of analytic laboratory error. Of these interferents, hemolysis is most frequently seen. And, while hemolysis mostly results from *in vitro* causes, other interferents are mostly associated with disease processes. Laboratory testing is usually quite precise, however, the problem of interference in testing is an ever-present problem. The shift to improve patient safety and medical communication requires that laboratory personnel identify laboratory errors and alert physicians to these errors. And, it is in this context that laboratory experts seek to push laboratories away from using crude, visual estimation to grade serum/plasma interferent indices to the more precise use of automated instrument-generated indices. Convincing laboratories to commit to these health care reform goals will result in less overall patient care errors and better-managed medical costs.

Keywords: laboratory error, serum/plasma analyte interference, health care reform, patient safety

REDUCING ANALYTIC LABORATORY ERROR TO IMPROVE PATIENT SAFETY AND TO REDUCE MEDICAL COSTS

Patient safety has come front and center in the desire to improve patient care, and clinical laboratory results have a direct influence on patient treatment. In 2008, the Centers for Disease Control and Prevention (CDC) commissioned a report with the desire to transform laboratory medicine by 2018. This report emphasizes laboratory testing and patient safety through the accurate reporting and interpretation of laboratory tests, which would, in effect, assist doctors in early disease diagnosis and treatment. It would also help them assess disease severity and the overall chance for patient recovery, and help them recognize the potential for unfavorable treatment responses (Sciacovelli & Plebani, 2009; Wolcott, 2008). In other words, a reduction in clinical laboratory error will lead to improvement in healthcare overall (Sciacovelli & Plebani, 2009).

Laboratory testing error is stratified into pre-analytic, analytic and post-analytic phases. Sample interference, which falls into the analytic phase of testing, represents ~7-13% of laboratory testing errors (Plebani, 2006). And, although clinical laboratory costs are relatively low (<5% of total managed care costs), decisions made from laboratory test results (i.e. admission, discharge and medication) influence additional costs in approximately two-thirds of cases (Lippi, Salvagno, Montagnana, Brocco, & Guidi, 2006; A. Simundic, Topic, Nikolac, & Lippi, 2010; A. M. Simundic et al., 2009). Therefore, in the design of analytical laboratory instruments, identification of potential interfering substances in blood is of utmost importance. Color or fluidity changes in serum/plasma are the usual culprits of laboratory analyte interference, which include hemolysis, icterus, turbidity, and viscosity.

In this review, we will discuss serum/plasma interferents, as they relate to disease processes and patient safety, and we will discuss how improved interferent detection will reduce healthcare costs and be aligned with the global goals of healthcare reform.

HEMOLYSIS

Hemolysis in blood samples results in release of free hemoglobin that interferes with many blood analyte measurements. Some analyte measurements can even be altered at hemoglobin concentrations below that which can be detected visually (0.6 g/dl) (Lippi et al., 2006).

Sample hemolysis results primarily from *in vitro* or pre-analytic error, and is, in fact, the main cause of unsuitable specimens in inpatient, outpatient and acute care settings (Lippi et al., 2008). *In vitro* hemolysis can be caused by a multitude of problems including: (1) blood drawn forcefully or blood drawn through small diameter needles, (2) blood drawn through partially obstructed catheters, (3) frozen or heated sample specimens, (4) under-filled collection tubes and (5) delayed separation of serum/plasma (Carraro, Servidio, & Plebani, 2000; Lippi et al., 2008). In vivo hemolysis is rarely encountered (~2% of all specimens), and can be caused by a variety of inherited defects, including sickle cell disease, thalassemias, pyruvate kinase deficiencies, and glucose-6-phosphate dehydrogenase deficiencies. In vivo hemolysis can also be seen in patients with acquired hemolytic anemias, such those with immune-mediated or autoimmune diseases, in burn victims, in patients with infections, such those with malaria, babesia, or clostridium infections, and in patients with damage to the cardiovascular system, such as those with hemolytic uremic syndrome, prosthetic cardiac valves and exposure to certain drugs or toxins (Lippi et al., 2008; Lippi, Plebani, Di Somma, & Cervellin, 2011).

ICTERUS

Icterus and jaundice are synonymous terms and define the yellow color in serum/plasma and skin/sclera that is associated with a plethora of diseases and syndromes (Burtis, Burtis, Ashwood, Bruns, & Sawyer, 2008). Icterus is caused by a build-up of bilirubin in blood (hyperbilirubinemia) and is associated with pre-hepatic, hepatic or post-hepatic problems (Beckingham & Krige, 2001; Beckingham & Ryder, 2001). Hyperbilirubinemia interferes with laboratory analyte measurements via spectral and chemical means (Kroll & Elin, 1994). Hemolytic diseases, as described above, and neonatal hyperbilirubinemia cause pre-hepatic icterus. Neonatal jaundice is present in many newborns without serious consequence and is due to a higher density of red blood cells and a slower conjugation and clearance of bilirubin compared to older children and adults (Moerschel, Cianciaruso, & Tracy, 2008).

Icterus associated liver disease has many causes. Viral diseases, primarily hepatitis A, B and C, result in acute illness with jaundice. Hepatitis A is transmitted via fecal-oral or direct contact and is usually self-limiting (World Health Organization, 2015a). Hepatitis B and C can cause both acute and chronic infections. Hepatitis B is most commonly seen in sub-Saharan Africa and East Asia where vaccinations are not available (World Health Organization, 2015b). Transmission is through body fluids, such as perinatal transmission and sexual contact (World Health Organization, 2015b, 2015c). Hepatitis C is found worldwide and is transmitted through blood and, is therefore, a common infection in IV drug users and persons requiring frequent blood transfusions (World Health Organization, 2015c). Liver cirrhosis, a frequent cause of icterus, is a chronic condition that results in the gradual replacement of normal liver tissue with abnormal fibrous tissue (Schuppan & Afdhal, 2008) It can be caused by Hepatitis B and C infections, severe alcohol consumption, and inherited disorders, such as Wilson's disease (accumulation of liver copper) or hemochromatosis (accumulation of liver iron). In addition, obesity can lead to nonalcoholic steatohepatitis that results in liver cirrhosis (Schuppan & Afdhal, 2008; World Health Organization, 2015b, 2015c). Liver cancer such as hepatocellular carcinoma or cholangiocarcinoma can also result in both hepatic and post-hepatic bilirubin accumulation (Brandi, Venturi, Pantaleo, Ercolani, & Gico, 2016; Dong & Saab, 2008). In addition, diseases of the gall bladder and common bile duct can cause post-hepatic bilirubin accumulation. These include cholangitis (inflammation of the gallbladder), cholecystitis (gallstone disease with inflammation), and choledocholithiasis (gall bladder and common bile duct gallstone disease) (Frossard et al., 2000; Strasberg, 2008; van Erpecum, 2006). And finally, pancreatic diseases, such as pancreatitis and pancreatic carcinoma are associated with obstructive jaundice (McCollum & Jordan, 1975; Swan, Bourke, Hopper, Kwan, & Williams, 2010).

TURBIDITY

Turbidity is the result of lipemia, which is the build up of chylomicrons (fat particles) in blood. Turbidity causes both light scattering and volume displacement problems during blood analyte measurements (Kroll & Elin, 1994). Lipemia is most commonly caused by blood drawn after a recent meal, and especially after a high fat and/or carbohydrate meal (Nikolac, 2014). Other causes include poorly controlled diabetes mellitus, hypothyroidism, obesity, extreme alcohol intake, some drugs, including estrogen and antiviral therapies, and a less common array of genetic disorders, such as familial combined hyperlipidemia, familial hypertriglyceridemia, and rarely dysbetalipoproteinemia. (Gan, Edwards, Symonds, & Beck, 2006; Julve, Martin-Campos, Escola-Gil, & Blanco-Vaca, 2016).

SERUM OR PLASMA HYPERVISCOSITY

High plasma or serum viscosity is usually associated with high paraproteins (monoclonal immunoglobulins or immunoglobulin light chains) (L. Cook & Macdonald, 2007). Serum/plasma hyperviscosity syndrome can develop from markedly increased paraproteins resulting in a triad of medical disturbances, specifically bleeding tendencies, retinal changes and neutrologic disturbances (Hernandez-Molina & Bermudez-Bermejo, 2015). These paraproteins interfere with variety of laboratory chemistry analyte and hematologic measurements with variable degrees of interference (Roy, 2009; Yang, Howanitz, Howanitz, Gorfajn, & Wong, 2008). Monoclonal gammopathies can be present in neoplastic diseases including multiple myeloma, amyloid light chains (AL) amyloidosis, chronic lymphocytic leukemia, Waldenstrom macroglobulinemia (lymphoplasmacytic leukemia), and solitary plasmacytoma. Monoclonal gammopathy of undetermined significance (MGUS) is a disorder with increased paraproteins, but without clonal B cell expansion, and is seen primarily in elderly individuals (L. Cook & Macdonald, 2007; Roy, 2009). In addition, increased paraproteins have been reported in three autoimmune diseases, namely rheumatoid

arthritis, Sjogren's syndrome and systemic lupus erythematosis for which hyperviscosity syndrome is occasionally present (Corrigan et al., 2010; Hernandez-Molina & Bermudez-Bermejo, 2015; Scofield et al., 1998). Finally, increased paraproteins can be seen in: (1) severe skin disease, such as pyoderma gangrenosum and necrobiotic xanthogranulomatosis; (2) Hashimoto's thyroiditis; (3) liver disease/cirrhosis; and (4) infectious diseases, such as mycobacterium tuberculosis and bacterial endocarditis (L. Cook & Macdonald, 2007).

REPORTS OF INTERFERENCE WITH AUTOMATED CHEMISTRY ANALYZER

Electrolytes are tightly controlled in the body and any true perturbations can have deleterious effects on patients. Therefore, being able to differentiate falsely increased or decreased electrolyte measurements is extremely important. Several cases of pseudohyperphosphatemia have been seen in people with multiple myeloma, which could be misconstrued as being due to tumor lysis syndrome or decreased renal function (Cheikhrouhou Abdelmoula, Amira, Chaabouni, Kchir, & Zouari, 2003; El Bouchti, Belkhou, Younsi, & El Asan, 2007; Larner, 1995; Lovekar & Chen, 2011). Pseudohyponatremia is frequently encountered with increased paraproteins and lipids and is due to a "volume exclusion effect" when using indirect potentiometry (Lippi & Aloe, 2010; A. W. Lyon & Baskin, 2003). As a case in point, a diabetic child, who presented to emergency, was both severely hyperlipidemic and hyponatremic. Pseudohyponatremia was missed and the patient was treated with 0.9% saline, which induced a hypernatremic state and accelerated the demise of the patient. (Frier, Steer, Baird, & Bloomfield, 1980). Finally, true hyperkalemia or hypokalemia can result in cardiac arrhythmias and can be life-threatening. Reverse pseudohyperkalemia is seen in leukemia/lymphoma patients when blood is drawn into lithium heparin tubes and it defines a situation where patients have falsely increased serum potassium levels, but serum potassium levels are actually normal. Masked hypokalemia occurs in hypokalemic patients who have serum/plasma potassium levels that fall into the normal reference interval, and it is usually seen with hemolysis, since red blood cells contain abundant intracellular potassium (Asirvatham, Moses, & Bjornson, 2013; Avelar, 2014; Mansoor, Holtzman, & Emadi, 2015).

Artificially increased bilirubin has also been associated with increased paraproteins, which could lead physicians to suspect that a patient has liver or hemolytic disease. In addition, artificially low high density lipoprotein (HDL) was also reported in a patient with increased paraproteins, which could lead to an erroneous assumption that the patient is at risk for cardiac disease (Dutta, 2012; Pantanowitz, Horowitz, Upalakalin, & Beckwith, 2003; Sheppard et al., 2005; Smogorzewska, Flood, Long, & Dighe, 2004).

Finally, erroneously low acetaminophen concentrations were present in an MGUS patient with increased paraproteins, and who overdosed on acetaminophen. The paraprotein interference made it difficult to monitor treatment of this patient (Hullin, 1999).

IMMUNOASSAYS AND REPORTS OF INTERFERENCE

There are principally two types of immunoassays, competitive and immunometric. Both involve antibody-antigen interactions; where competitive assays have antigen stabilized on a substrate, and antibodies of interest attach to the antigen, and immunometric assays have a sandwich configuration with two antibodies, one coupled to a solid substrate with the objective of capturing antigen and the other directed at another site on the antigen, which has a signal attached. Antibodies that have lower affinity for the antigen are frequently used in these assays (Klee, 2004). Analytes measured using immunoassays include hormones, tumor markers, drugs, cardiac markers, and microbial antigens. Both analyte-independent and analyte-dependent interferences exist. Analyte-independent interferences include hemolysis and lipemia. Analyte-dependent interferences include cross-reacting antibodies, such as heterophile, human anti-animal, and rheumatoid factor antibodies, plus a host of other proteins (Tate & Ward, 2004).

The main immunoassay interferences come from cross-reacting heterophilic polyclonal antibodies, and while these interferences are important, they are not the focus of this review (Tate & Ward, 2004). Hemolysis has been shown to cause significant and negative interference for Vitamin B12, testosterone, cortisol and cardiac troponin T measurements that become more pronounced as the hemolysis index increases (Cemin & Daves, 2015; M. E. Lyon, Ball, Krause, Slotsve, & Lyon, 2004; Snyder et al., 2004). A recent study by Moalem et al, demonstrated that hemolysis has a significant negative interference with parathyroid hormone (PTH) measurements. During surgical removal of parathyroid tumors in people with primary hyperparathyroidism, intraoperative-PTH measurements are taken and compared to the pre-operative test measurements. PTH is expected to decline from the pre-test measurement, however, problems could arise if either the pre- or post-blood samples are hemolyzed. For instance, if the pre-surgical blood test shows a falsely low PTH due to hemolysis and the intra-operative blood test generates a correct PTH, then surgery might be extended due to the assumption that hyperfunctioning tissue is still present. On the contrary, if the pre-PTH is correct, but the intraoperative PTH is falsely low due to hemolysis, then surgery may be completed without removing all the tumor tissue, thus requiring additional surgeries (Moalem et al., 2010). In another case, a patient with a history of gastroesophageal reflux presented complaining of chest pain. Serum cardiac troponin, a marker for cardiac disease, was increased resulting in cardiac catheterization, and it was only later that the increase in cardiac troponin was realized to be secondary to hemolysis (Masimasi & Means, 2005). Moderate hemolysis has also been shown to negatively interfere with insulin assays and is caused by the release of insulin degradation enzymes from red blood cells (P. R. Cook, Glenn, & Armston, 2010; D'Costa, Feld, Laxdal, Trundle, & Collinsworth, 1993).

Although high plasma paraproteins and hyperviscosity can lead to frequent spurious results on automated chemistry analyzers, more data is needed to address the effects of these complications on patient outcomes especially in relation to immunoassay platforms.

Paraproteinemia has been shown to cause erroneous thyroxine immunoassay results with both positive and negative interferences; these discrepancies were likely the result of different assay formats (Alexander, Gattra, & Nishimoto, 1980; Tamagna, Hershman, & Premachandra, 1979). More recently, paraprotein interference was documented in turbidometric drug assays for gentamicin, valproate and vancomycin due to precipitation of IgM paraproteins (Dimeski, Bassett, & Brown, 2015). And in another interesting case of interference, a 58-year old woman with MGUS had a positive serum C-reactive protein (CRP) suggesting underlying inflammation. For more that 2 1/2 years, and after numerous tests and eight potential diagnoses, the patient was referred to an infectious disease clinic, where it was discovered that the increased CRP was due to interference and thus, the patient required no further workup (Daly, Cartwright, Lehner, & Javid, 2008).

HEALTH CARE REFORM AND ANALYTIC LABORATORY ERROR

In 2000, the Institute of Medicine (US) Committee on Quality of Health Care in America galvanized the health care industry by exposing medical errors and putting forth a challenge to improve patient safety (Kohn, 2000). Soon after, England and Canada published similar reports on patient safety, which was followed by the formation of the world health organization (WHO) International Alliance of Patient Safety in 2004 (British Department of Health, 2007; Donaldson, 2004; Kohn, 2000; Wade, 2002). And although these reports did not specifically discuss laboratory error, it set the course for the CDC's report on laboratory medicine 4 years later (Wolcott, 2008).

In 2012, the International Federation of Clinical Chemistry task force on the Impact of Laboratory Medicine on Clinical Management and Outcomes was formed to identify the impact of laboratory medicine in overall health care, and to design studies that reveal ways in which laboratory medicine could improve patient outcomes. This task force concluded that, from current evidence, the true impact of laboratory medicine was difficult to assess due to the complexity of patient care and to the lack of studies that show clinical efficacy in diagnostic test result interpretation. In other words, more studies are needed to assess if a test actually improves patient outcomes (Hallworth et al., 2015).

It is obvious, from this review, that all of the cases mentioned would have had additional workups due to laboratory interference. In one study, the estimated cost of re-testing in their institution was approximately $23,000 in patient charges per year (Khodorkovsky, Cambria, Lesser, & Hahn, 2014). In the United States alone, there are more than 5600 hospitals for which excess charges, in the realm of $129 million in patient charges per year, are possible (American Hospital Association, 2016). However, Zhi et al. suggested that re-testing is not the only problem in laboratory medicine. They performed meta-analysis and examined tests that should have been run, but were not (underutilized tests) and tests that were run, but were not indicated (overutilized tests). They found that underutilized laboratory test rates were higher (44.8%) than overutilized test rates (20.6%), which points to problems in both patient safely and health care costs (Zhi, Ding, Theisen-Toupal, Whelan, & Arnaout, 2013).

One area of concern involves the process of visually grading hemolysis and icterus, which occurs in many laboratories worldwide. Several studies and reviews have determined that grading these indices using visual inspection is substandard to using automated analyzer measurements (Glick, Ryder, Glick, & Woods, 1989; A. Simundic et al., 2010). In fact, in 2004, a study demonstrated that when an automated detection system replaced a visual detection system, serum/plasma hemolysis, icterus, and turbidity detection improved 67-fold, 10-fold and 1012-fold, respectively. (Vermeer, Thomassen, & de Jonge, 2005). Experts in health care reform and laboratory medicine agree that visual detection of hemolysis is random and mostly unreliable even by the most experience technologists, resulting in over- or underestimation of hemolysis (Howanitz, Lehman, Jones, Meier, & Horowitz, 2015; Lippi et al., 2011; Smith et al., 2012). In addition, visual inspection cannot identify the combinations of interfering substance that may be present in a sample (Howanitz et al., 2015). Therefore, it has been put forth that automated analyzers be used for standard assessment of these indices and that consistent reporting of laboratory results be executed to reduce inter-laboratory variability. And, in addition to hemolysis, icterus, and turbidity/lipemia, serum/plasma viscosity can also be estimated, providing information on paraprotein interference, to those laboratories using the VITROS® chemistry and immunoassay analyzers (Ortho Clinical Diagnostics) (Ding, 2015).

Hallworth et al. estimated that the global *in vitro* market would grow to about $52 billion by 2017, which corresponds to 10-15 billion laboratory tests. And, since so many laboratory tests are and will be generated, laboratory experts wish to improve physician-laboratory and physician-patient relationships (called the Brain-to-Brain Loop), in the hope of improving patient outcomes to risks associated with laboratory tests and interpretation of those tests (Plebani, Laposata, & Lundberg, 2011). Expected areas of improvement would include decreases in: (1) unnecessary hospital admissions, (2) delay of care due to repeated tests, (3) medication errors due to misinterpretation of laboratory results, and (4) inappropriate discharge timing and instructions.

CONCLUSIONS

In order to comply with health care reform and patient safety, laboratories worldwide should become aware of the most precise diagnostic methods available. And while analytical interference is only a small part of the overall problem facing health care, precision in diagnostic testing, detail in diagnostic reporting and communication of possible interferents is necessary to protect patients. In summary, automated detection of hemolysis, icterus, turbidity, and viscosity indices on all serum/plasma samples should be performed to reduce laboratory error, improve test result turnaround time, improve patient care, decrease costs and generate measurable and repeatable data for future patient outcome studies.

References

1. Alexander, N. M., Gattra, R., & Nishimoto, M. (1980). Myeloma immunoglobulin interferes with serum thyroxine analysis by homogeneous enzyme immunoassay. *Clin Chim Acta, 100*(3), 301-305.
2. American Hospital Association. (2016). Fast Facts on US Hospitals. Retrieved from http://www.aha.org/research/rc/stat-studies/fast-facts.shtml
3. Asirvatham, J. R., Moses, V., & Bjornson, L. (2013). Errors in potassium measurement: a laboratory perspective for the clinician. *N Am J Med Sci, 5*(4), 255-259. doi:10.4103/1947-2714.110426
4. Avelar, T. (2014). Reverse pseudohyperkalemia in a patient with chronic lymphocytic leukemia. *Perm J, 18*(4), e150-152. doi:10.7812/TPP/14-084
5. Beckingham, I. J., & Krige, J. E. (2001). ABC of diseases of liver, pancreas, and biliary system: Liver and pancreatic trauma. *BMJ, 322*(7289), 783-785.
6. Beckingham, I. J., & Ryder, S. D. (2001). ABC of diseases of liver, pancreas, and biliary system. Investigation of liver and biliary disease. *BMJ, 322*(7277), 33-36.
7. Brandi, G., Venturi, M., Pantaleo, M. A., Ercolani, G., & Gico. (2016). Cholangiocarcinoma: Current opinion on clinical practice diagnostic and therapeutic algorithms: A review of the literature and a long-standing experience of a referral center. *Dig Liver Dis, 48*(3), 231-241. doi:10.1016/j.dld.2015.11.017
8. British Department of Health. (2007). *Building a safer NH for patients, implementing an organisation with a memory*. London, England Retrieved from http://webarchive.nationalarchives.gov.uk/20040117013247/http://www.doh.gov.uk/buildsafenhs/buildsafenhs.pdf.
9. Burtis, C. A., Burtis, C. A., Ashwood, E. R., Bruns, D. E., & Sawyer, B. G. (2008). *Tietz fundamentals of clinical chemistry* (6th ed.). St. Louis, Mo.: Saunders/Elsevier.
10. Carraro, P., Servidio, G., & Plebani, M. (2000). Hemolyzed specimens: a reason for rejection or a clinical challenge? *Clin Chem, 46*(2), 306-307.
11. Cemin, R., & Daves, M. (2015). Pre-analytic variability in cardiovascular biomarker testing. *J Thorac Dis, 7*(10), E395-401. doi:10.3978/j.issn.2072-1439.2015.10.03
12. Cheikhrouhou Abdelmoula, L., Amira, C., Chaabouni, L., Kchir, M. M., & Zouari, R. (2003). Hyperphosphatemia in multiple myeloma. *Joint Bone Spine, 70*(6), 541-542.
13. Cook, L., & Macdonald, D. H. (2007). Management of paraproteinaemia. *Postgrad Med J, 83*(978), 217-223. doi:10.1136/pgmj.2006.054627
14. Cook, P. R., Glenn, C., & Armston, A. (2010). Effect of hemolysis on insulin determination by the Beckman Coulter Unicell DXI 800 immunoassay analyzer. *Clin Biochem, 43*(6), 621-622. doi:10.1016/j.clinbiochem.2010.01.002
15. Corrigan, F. E., 3rd, Leventhal, A. R., Khan, S., Rao, S., Christopher-Stine, L., & Schulman, S. P. (2010). A rare cause of cardiac ischemia: systemic lupus erythematosus presenting as the hyperviscosity syndrome. *Ann Intern Med, 153*(6), 422-424. doi:10.7326/0003-4819-153-6-201009210-00023
16. D'Costa, M., Feld, R., Laxdal, V., Trundle, D., & Collinsworth, W. L. (1993). A multicenter evaluation of the Boehringer Mannheim ES 300 immunoassay system. *Clin Biochem, 26*(1), 51-57.
17. Daly, M. L., Cartwright, D. J., Lehner, P. J., & Javid, B. (2008). A 58-year-old woman with abdominal symptoms and elevated C-reactive protein. *PLoS Med, 5*(7), e149. doi:10.1371/journal.pmed.0050149
18. Dimeski, G., Bassett, K., & Brown, N. (2015). Paraprotein interference with turbidimetric gentamicin assay. *Biochem Med (Zagreb), 25*(1), 117-124. doi:10.11613/BM.2015.014
19. Ding, Z. (2015, Aug 12, 2015). Method for estimating viscosity *Google Patents.* Retrieved from https://www.google.com.ar/patents/EP2378265A3?cl=en
20. Donaldson, L. (2004). International Alliance of Patient Safety in 2004 Retrieved from http://www.who.int/patientsafety/international_alliance/en/
21. Dong, M. H., & Saab, S. (2008). Complications of cirrhosis. *Dis Mon, 54*(7), 445-456. doi:10.1016/j.disamonth.2008.03.006
22. Dutta, A. K. (2012). A curious case of hyperbilirubinemia. *Indian J Clin Biochem, 27*(2), 200-201. doi:10.1007/s12291-011-0160-0
23. El Bouchti, I., Belkhou, A., Younsi, R., & El Asan, S. (2007). Pseudohyperphosphatemia in multiple myeloma. *Joint Bone Spine, 74*(2), 206-207. doi:10.1016/j.jbspin.2006.07.004
24. Frier, B. M., Steer, C. R., Baird, J. D., & Bloomfield, S. (1980). Misleading plasma electrolytes in diabetic children with severe hyperlipidaemia. *Arch Dis Child, 55*(10), 771-775.
25. Frossard, J. L., Hadengue, A., Amouyal, G., Choury, A., Marty, O., Giostra, E.,... Amouyal, P. (2000). Choledocholithiasis: a prospective study of spontaneous common bile duct stone migration. *Gastrointest Endosc, 51*(2), 175-179.
26. Gan, S. I., Edwards, A. L., Symonds, C. J., & Beck, P. L. (2006). Hypertriglyceridemia-induced pancreatitis: A case-based review. *World J Gastroenterol, 12*(44), 7197-7202.
27. Glick, M. R., Ryder, K. W., Glick, S. J., & Woods, J. R. (1989). Unreliable visual estimation of the incidence and amount of turbidity, hemolysis, and icterus in serum from hospitalized patients. *Clin Chem, 35*(5), 837-839.
28. Hallworth, M. J., Epner, P. L., Ebert, C., Fantz, C. R., Faye, S. A., Higgins, T. N.,... Outcomes. (2015). Current evidence and future perspectives on the effective practice of patient-centered laboratory medicine. *Clin Chem, 61*(4), 589-599. doi:10.1373/clinchem.2014.232629
29. Hernandez-Molina, G., & Bermudez-Bermejo, P. (2015). Hyperviscosity in primary Sjogren's syndrome: clinical implications. *Int J Rheum Dis*. doi:10.1111/1756-185X.12751
30. Howanitz, P. J., Lehman, C. M., Jones, B. A., Meier, F. A., & Horowitz, G. L. (2015). Practices for Identifying and Rejecting Hemolyzed Specimens Are Highly Variable in Clinical Laboratories. *Arch Pathol Lab Med, 139*(8), 1014-1019. doi:10.5858/arpa.2014-0161-CP
31. Hullin, D. A. (1999). An IgM paraprotein causing a falsely low result in an enzymatic assay for acetaminophen. *Clin Chem, 45*(1), 155-157.
32. Julve, J., Martin-Campos, J. M., Escola-Gil, J. C., & Blanco-Vaca, F. (2016). Chylomicrons: Advances in biology, pathology, laboratory testing, and therapeutics. *Clin Chim Acta, 455*, 134-148. doi:10.1016/j.cca.2016.02.004

References (continued)

33. Khodorkovsky, B., Cambria, B., Lesser, M., & Hahn, B. (2014). Do hemolyzed potassium specimens need to be repeated? *J Emerg Med, 47*(3), 313-317. doi:10.1016/j.jemermed.2014.04.019

34. Klee, G. G. (2004). Interferences in hormone immunoassays. *Clin Lab Med, 24*(1), 1-18. doi:10.1016/j.cll.2004.01.003

35. Kohn, L. T., Corrigan, J.M., Donaldson, M.S. (2000). *To Err Is Human: Building a Safer Health System*. Washington, D.C.: NATIONAL ACADEMY PRESS.

36. Kroll, M. H., & Elin, R. J. (1994). Interference with clinical laboratory analyses. *Clin Chem, 40*(11 Pt 1), 1996-2005.

37. Larner, A. J. (1995). Pseudohyperphosphatemia. *Clin Biochem, 28*(4), 391-393.

38. Lippi, G., & Aloe, R. (2010). Hyponatremia and pseudohyponatremia: first, do no harm. *Am J Med, 123*(9), e17. doi:10.1016/j.amjmed.2010.03.020

39. Lippi, G., Blanckaert, N., Bonini, P., Green, S., Kitchen, S., Palicka, V.,... Plebani, M. (2008). Haemolysis: an overview of the leading cause of unsuitable specimens in clinical laboratories. *Clin Chem Lab Med, 46*(6), 764-772. doi:10.1515/CCLM.2008.170

40. Lippi, G., Plebani, M., Di Somma, S., & Cervellin, G. (2011). Hemolyzed specimens: a major challenge for emergency departments and clinical laboratories. *Crit Rev Clin Lab Sci, 48*(3), 143-153. doi:10.3109/10408363.2011.600228

41. Lippi, G., Salvagno, G. L., Montagnana, M., Brocco, G., & Guidi, G. C. (2006). Influence of hemolysis on routine clinical chemistry testing. *Clin Chem Lab Med, 44*(3), 311-316. doi:10.1515/CCLM.2006.054

42. Lovekar, S., & Chen, J. L. (2011). A 90-year-old man with hyperphosphatemia. *Am J Kidney Dis, 57*(2), 342-346. doi:10.1053/j.ajkd.2010.07.017

43. Lyon, A. W., & Baskin, L. B. (2003). Pseudohyponatremia in a Myeloma Patient: Direct Electrode Potentiometry is a Method Worth its Salt. *Laboratory Medicine, 34*(5), 57 - 60.

44. Lyon, M. E., Ball, C. L., Krause, R. D., Slotsve, G. A., & Lyon, A. W. (2004). Effect of hemolysis on cardiac troponin T determination by the Elecsys 2010 immunoanalyzer. *Clin Biochem, 37*(8), 698-701. doi:10.1016/j.clinbiochem.2004.03.002

45. Mansoor, S., Holtzman, N. G., & Emadi, A. (2015). Reverse Pseudohyperkalemia: An Important Clinical Entity in Chronic Lymphocytic Leukemia. *Case Rep Hematol, 2015*, 930379. doi:10.1155/2015/930379

46. Masimasi, N., & Means, R. T., Jr. (2005). Elevated troponin levels associated with hemolysis. *Am J Med Sci, 330*(4), 201-203.

47. McCollum, W. B., & Jordan, P. H. (1975). Obstructive jaundice in patients with pancreatitis without associated biliary tract disease. *Ann Surg, 182*(2), 116-120.

48. Moalem, J., Ruan, D. T., Farkas, R. L., Shen, W. T., Miller, S., Duh, Q. Y.,... Kebebew, E. (2010). Prospective evaluation of the rate and impact of hemolysis on intraoperative parathyroid hormone (IOPTH) assay results. *Ann Surg Oncol, 17*(11), 2963-2969. doi:10.1245/s10434-010-1161-6

49. Moerschel, S. K., Cianciaruso, L. B., & Tracy, L. R. (2008). A practical approach to neonatal jaundice. *Am Fam Physician, 77*(9), 1255-1262.

50. Nikolac, N. (2014). Lipemia: causes, interference mechanisms, detection and management. *Biochem Med (Zagreb), 24*(1), 57-67. doi:10.11613/BM.2014.008

51. Pantanowitz, L., Horowitz, G. L., Upalakalin, J. N., & Beckwith, B. A. (2003). Artifactual hyperbilirubinemia due to paraprotein interference. *Arch Pathol Lab Med, 127*(1), 55-59. doi:10.1043/0003-9985(2003)127<55:AHDTP>2.0.CO;2

52. Plebani, M. (2006). Errors in clinical laboratories or errors in laboratory medicine? *Clin Chem Lab Med, 44*(6), 750-759. doi:10.1515/CCLM.2006.123

53. Plebani, M., Laposata, M., & Lundberg, G. D. (2011). The brain-to-brain loop concept for laboratory testing 40 years after its introduction. *Am J Clin Pathol, 136*(6), 829-833. doi:10.1309/AJCPR28HWHSSDNON

54. Roy, V. (2009). Artifactual laboratory abnormalities in patients with paraproteinemia. *South Med J, 102*(2), 167-170. doi:10.1097/SMJ.0b013e3181831f6a

55. Schuppan, D., & Afdhal, N. H. (2008). Liver cirrhosis. *Lancet, 371*(9615), 838-851. doi:10.1016/S0140-6736(08)60383-9

56. Sciacovelli, L., & Plebani, M. (2009). The IFCC Working Group on laboratory errors and patient safety. *Clin Chim Acta, 404*(1), 79-85. doi:10.1016/j.cca.2009.03.025

57. Scofield, R. H., Tardibono, G., Ogden, S. B., Harley, J. B., Reichlin, M., & Kurien, B. T. (1998). Rheumatoid hyperviscosity: analysis of a patient with intermediate complexes that block other autoantibodies and a review of the literature. *Semin Arthritis Rheum, 27*(6), 382-391.

58. Sheppard, C. A., Allen, R. C., Austin, G. E., Young, A. N., Ribeiro, M. A., & Fantz, C. R. (2005). Paraprotein interference in automated chemistry analyzers. *Clin Chem, 51*(6), 1077-1078. doi:10.1373/clinchem.2004.045740

59. Simundic, A., Topic, E., Nikolac, N., & Lippi, G. (2010). Hemolysis detection and management of hemolyzed specimens. *Biochemia Medica, 20*(2), 154-159.

60. Simundic, A. M., Nikolac, N., Ivankovic, V., Ferenec-Ruzic, D., Magdic, B., Kvaternik, M., & Topic, E. (2009). Comparison of visual vs. automated detection of lipemic, icteric and hemolyzed specimens: can we rely on a human eye? *Clin Chem Lab Med, 47*(11), 1361-1365. doi:10.1515/CCLM.2009.306

61. Smith, M. B., Chan, Y. W., Dolci, A., Kellogg, M. D., McCudden, C. R., McLean, M.,... Zakowski, J. (2012). *Hemolysis, Icterus, and Lipemia/Turbidity Indices as Indicators of Interference in Clinical Laboratory Analysis; Approved Guideline* Vol. 32. (pp. 1-14).

62. Smogorzewska, A., Flood, J. G., Long, W. H., & Dighe, A. S. (2004). Paraprotein interference in automated chemistry analyzers. *Clin Chem, 50*(9), 1691-1693. doi:10.1373/clinchem.2004.037499

63. Snyder, J. A., Rogers, M. W., King, M. S., Phillips, J. C., Chapman, J. F., & Hammett-Stabler, C. A. (2004). The impact of hemolysis on Ortho-Clinical Diagnostic's ECi and Roche's elecsys immunoassay systems. *Clin Chim Acta, 348*(1-2), 181-187. doi:10.1016/j.cccn.2004.05.017

64. Strasberg, S. M. (2008). Clinical practice. Acute calculous cholecystitis. *N Engl J Med, 358*(26), 2804-2811. doi:10.1056/NEJMcp0800929

References (continued)

65. Swan, M. P., Bourke, M. J., Hopper, A. D., Kwan, V., & Williams, S. J. (2010). Autoimmune pancreatitis: an important diagnostic consideration in obstructive jaundice due to a pancreatic mass lesion. *Intern Med J, 40*(10), 720-725.

66. Tamagna, E., Hershman, J., & Premachandra, B. N. (1979). Circulating thyroid hormones in a patient with hyperviscosity syndrome. *Clin Chim Acta, 93*(2), 263-268.

67. Tate, J., & Ward, G. (2004). Interferences in immunoassay. *Clin Biochem Rev, 25*(2), 105-120.

68. van Erpecum, K. J. (2006). Gallstone disease. Complications of bile-duct stones: Acute cholangitis and pancreatitis. *Best Pract Res Clin Gastroenterol, 20*(6), 1139-1152. doi:10.1016/j.bpg.2006.03.012

69. Vermeer, H. J., Thomassen, E., & de Jonge, N. (2005). Automated processing of serum indices used for interference detection by the laboratory information system. *Clin Chem, 51*(1), 244-247. doi:10.1373/clinchem.2004.036301

70. Wade, J. (2002). *Building a Safer System: A National Integrated Strategy for Improving Patient Safety in Canadian Health Care*. Saskatchewan: The Royal College of Physicians and Surgeons of Canada Retrieved from http://www.royalcollege.ca/portal/page/portal/rc/common/documents/advocacy/building_a_safer_system_e.pdf.

71. Wolcott, J., Schwartz, A., Goodman, C. (2008). *Laboratory Medicine: A National Status Report* Retrieved from:
World Health Organization. (2015a). Hepatitis A Retrieved from http://www.who.int/mediacentre/factsheets/fs328/en/
World Health Organization. (2015b). Hepatitis B. Retrieved from http://www.who.int/mediacentre/factsheets/fs204/en/
World Health Organization. (2015c). Hepatitis C. Retrieved from http://www.who.int/entity/mediacentre/factsheets/fs164/en/

72. Yang, Y., Howanitz, P. J., Howanitz, J. H., Gorfajn, H., & Wong, K. (2008). Paraproteins are a common cause of interferences with automated chemistry methods. *Arch Pathol Lab Med, 132*(2), 217-223. doi:10.1043/1543-2165(2008)132[217:PAACCO]2.0.CO;2

73. Zhi, M., Ding, E. L., Theisen-Toupal, J., Whelan, J., & Arnaout, R. (2013). The landscape of inappropriate laboratory testing: a 15-year meta-analysis. *PLoS One, 8*(11), e78962. doi:10.1371/journal.pone.0078962

This work was funded by Ortho Clinical Diagnostics. © 2016 Ortho Clinical Diagnostics PR-02141