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Review article
Pregledni članak

IMPROVING THE PREANALYTICAL PROCESS: THE FOCUS ON SPECIMEN QUALITY

POBOLJŠANJE PREANALITIČKOG PROCESA: FOKUSIRANJE NA KVALITET UZORKA

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Summary: Trends in clinical laboratory practice place more demands on the quality of patient specimens. Advances in analytical performance (i.e., increased automation, reduced sample volume, increased assay sensitivity), as well as efficiency and cost reduction gains (i.e., throughput, test turnaround time) have improved medical practice. These changes, however, have caused an increased incidence of preanalytical errors, dictating the need for higher-quality specimens. The following paper addresses these errors in addition to methodologies for improving the quality of the preanalytical phase.

Keywords: preanalytical errors, laboratory automation, specimen quality, analytical process, Lean, Six Sigma

Kratak sadržaj: Trendovi u kliničkoj laboratorijskoj praksi postavljaju više zahteva za kvalitet uzoraka pacijenata. Unapređenje analitičkih karakteristika (npr. povećanje automatizacije, smanjenje zapremine uzorka, povećanje osetljivosti određivanja), kao i efikasnost i smanjenje troškova (npr. prohodnost, vreme obrta testova) unapredilo je medicinsku praksu. Međutim, te promene su izazvale povećanje incidencije preanalitičkih grešaka što nameće potrebu za uzorcima većeg kvaliteta. Sledeći članak govori o tim greškama kao i o metodologijama za poboljšanje kvaliteta preanalitičke faze.

Ključne reči: preanalitičke greške, laboratorijska automatizacija, kvalitet uzorka, analitički proces, *Lean, Six Sigma*

Introduction

Clinical laboratories have witnessed major changes due to technological progress and economic demands (1). Advancements in the analytical phase of testing such as laboratory automation, reduced sample volumes, and requests for high-sensitivity assays are supplemented by requirements for rapid turnaround time and cost reduction. Accordingly, these technologies warrant the collection of higher-quality specimens to ensure optimal results.

While the majority of attention has been focused on the analytical process, consideration should also be applied to the preanalytical phase as well, as this process affects the reliability of test results, consuming valuable healthcare resources and possibly compromising treatment outcomes (2). For example, samples are more frequently transported, often at longer distances, for enhanced efficiency as laboratories and hospitals merge; simultaneously, advances in medical practice have driven an increase in test menus, new analytical methods and instruments. These changes subject specimens to variables (e.g., time, temperature, and vibration), which can affect sample quality.

Quality, effectiveness, and impact on outcomes continue to emerge as crucial value-added services for the laboratory (1). Hence, the implementation of a comprehensive quality control program, coupled with preanalytical education and Lean and Six Sigma methodologies, offers valuable tools to improve specimen quality and, subsequently, patient care. These services are discussed in the following article.

Laboratory Automation

Laboratory automation systems require the use of high-quality specimen containers to ensure throughput efficiencies. The collection tube's external characteristics such as tube taper, tube stopper material, and

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integrity of tube closure play a major role in achieving a higher-quality specimen. Small variations in tube dimensions, stopper pull-out forces, and cap pierceability due to stopper density may affect instrument efficiency and down time. Quality is also critical inside of the tube. It is the responsibility of tube manufacturers to incorporate accurate and precise amounts of additives. Conversely, the laboratory/phlebotomist must ensure proper collection, mixing, centrifugation and handling conditions, which can also affect specimen quality. Time constraints and increased workflow often result in less visual verification of specimen quality.

Reduced Sample Volumes

Many modern analyzers aspirate less than 5 μL of the specimen. In order to avoid probe gel issues, some new instruments have level sensors and pipette from the sample meniscus. Additionally, the presence of small amounts of low-density matter (e.g., fibrin, cell aggregates) can float to the top of the sample. Therefore, the first pipetted sample may collect material that is not representative of the patient's serum or plasma. The second, third, or subsequent samples may then provide a different result that is more characteristic of the patient's blood than that seen in the first sample. Mixing can homogenize the sample by breaking the interfering film at the meniscus. Hence, it is essential for laboratory professionals to maximize specimen quality by complying with best practices in blood collection, specimen transportation and handling, and by using premium blood collection devices with appropriate tube characteristics (i.e., tube taper, tube stopper material, integrity of tube closure, tube dimensions, stopper pull-out forces).

High-Sensitivity Assays

The request for high-sensitivity assays »raises the bar« for high-quality specimens. In the past, detection limits were at nanomole (10^{-9}M) and picomole (10^{-12}M) concentrations. It is now possible to measure even lower concentrations of analytes at femtomole (10^{-15}M), attomole (10^{-18}M) and at times zeptomole (10^{-21}M) and yoctomole (10^{-24}M). Therefore, any change to specimen collection protocols (i.e., consumables, such as blood collection tubes or specimen handling practices) must be validated prior to implementation. In addition, many instrument manufacturers validate their assays on only one or two tube types from a single tube manufacturer, and the validation process may be limited to control materials and healthy blood donors, as opposed to patient blood samples typically found in a hospital setting. Therefore, whenever changing any manufacturer's blood collection tube type, size or storage condition for a particular laboratory assay, laboratory personnel should review the tube manufacturer's data as well as their own data to establish/verify the reference range for a specific instrument/reagent system. Based on this information, the laboratory can decide if a change is appropriate.

Rapid Turnaround Time

The need for rapid turnaround time is critical in the Emergency Department and acute care settings in the hospital. The often chaotic and unpredictable environment in these sections of the hospital, however, may contribute to suboptimal quality specimens. Rushed phlebotomy techniques and catheter collections may result in hemolysis, increased sample fibrin, inadequate sample mixing, delays in transport, incomplete fill volume, incomplete clotting and serum collected from patients who are on heparin therapy. A decrease in centrifugation time also may lead to cellular contamination of the serum specimen as well as incomplete barrier formation. In addition, cost-cutting measures may result in laboratory mergers and increased transport time as well as increased sample exposure to extreme temperatures, humidity and vibration.

Conserving Resources

The demands to conserve time and reduce costs often result in a lack of sufficient education/training and subsequent noncompliance with safety measures. These variables play a role in the impact of suboptimal quality on test errors and clinical outcomes as well as the potential to compromise the safety of the patient and healthcare worker. Additionally, lower quality products may adversely affect specimen quality and increase specimen rejection rates. The consequences of these factors ultimately increase financial requirements due to repeat testing and test result errors as well as adverse patient outcomes and possible prolonged hospital stays as demonstrated in *Table I*.

Specimen Quality, Laboratory Errors and Effect on Outcomes

While the importance of monitoring every step in laboratory testing to identify defects has been acknowledged, most of the efforts have been focused on the analytical phase of the testing process (3). As documented in the literature, these efforts have resulted in a low percentage of errors in the analytical phase, however, with a higher percentage recorded in the preanalytical and postanalytical phases: analytical 7%, preanalytical 46%, postanalytical 47% (4). The impact of these errors was confirmed by a study conducted by Plebani and Carraro at the University Hospital of Padova, Italy, which evaluated medical outcomes as a result of preanalytical errors (*Table II*) (4).

Table I Preanalytical factors and impact on patients and healthcare institutions.

Common Preanalytical Errors	Impact on Patients	Impact on Healthcare Institutions
Hemolysis Underfilled blood collection tubes Clotted blood samples/ improper mixing Sample collection from incorrect patient Erroneous labeling of specimens	If error is not detected: Misdiagnosis Improper treatment/therapy Inappropriate blood transfusion (Can be fatal)	Prolonged or unnecessary hospital stays due to inappropriate treatment Increased cost of staff, resources for improper investigations and lab testing Possible legal action due to serious or fatal medical errors
	If error is detected: Additional pain and discomfort due to multiple blood collections Delay in appropriate treatment/therapy	Increased cost of staff time and consumables for redrawing of samples Increased staff time for maintenance of costly lab equipment, increased downtime of analyzers and delays in overall turnaround time

Table II Medical outcomes as a result of laboratory errors (4).

- 74% of preanalytical errors had no patient impact
- 26% had significant impact on patient outcome
  - 19.6% of errors caused further improper investigations
  - 6.4% of errors were associated with inappropriate care or:
    - 2.2% – inappropriate transfusion
    - 2.2% – inappropriate change of heparin infusion
    - 1.0% – inappropriate electrolyte administration
    - 1.0% – inappropriate change in digoxin dose

The High Cost of Laboratory Errors

The following case studies were conducted by BD to assess the impact of laboratory errors on a hospital's resources.

Case 1

Based on the study by Plebani and Carraro (4), error data were extrapolated from a 495-bed hospital in Ontario, Canada. According to that study, 68.2% of errors would occur during the preanalytical process (based on 12,485 tests on 694 patients); 19% of these errors would be clinically significant (198 patients); 6.4% would impact the patient and result in improper care and/or modification of therapy (67 patients). These errors would also create a financial burden for the hospital (*Table III*).

Table III Bearing the Burden of Preanalytical Errors.

Total Annual Cost of Preanalytical Errors to a 495-Bed Hospital	**$981,139**
Cost does not include trauma suffered by the patient	**unknown cost**

Clinically significant adverse events extend average hospital stay by: (projected)	2 days
Average cost of 1-day hospital stay in Ontario	$800
Total cost of the additional length of stay	$316,281
5 additional lab investigations due to preanalytical adverse event	$24,709
Other expenses due to investigations (projected)	$39,535
Total cost of clinically significant preanalytical adverse events	**$380,525**

Preanalytical adverse events due to inappropriate care or therapy extend average length of stay by:	6 days
Average cost of 1-day hospital stay in Ontario	$800
Total cost of the additional length of stay	$319,610
18 additional lab investigations due to preanalytical adverse events	$9,988
Other expenses due to investigations (projected)	$79,903
Medication expenses per treatment (projected)	$9,988
Total cost of improper care or therapy due to preanalytical errors (projected)	**$419,489**

Number of tubes used	1,750,000
Average redraw frequency (projected)	262,500
Cost of equipment for redraw	$181,125
FTE hours spent collecting redraws (2 tubes at 15 min/redraw)	32,813

Case 2

In addition to financial considerations, preanalytical errors drain staff resources due to specimen redraws (5) as demonstrated by a study conducted at a community hospital. Redraws were requested on each of the 1,014 samples rejected within a time period of two months. Of these, 37.7% of the rejected specimens were from the Emergency Department, 23.6% from the Medical Units, and 20.7% from the Surgical

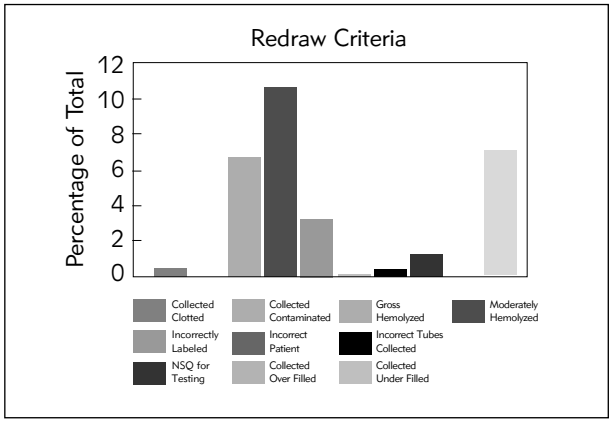

Figure 1 Redraw criteria as a result of specimen rejection, with hemolysis as a major factor.

Units. The majority of the specimens were rejected due to underfilling, incorrect labeling, or moderate or gross hemolysis (*Figure 1*).

Supporting Preanalytical Improvement

Conversion to a Closed Collection System

The conversion to a closed blood collection system may assist in reducing preanalytical errors. Standardization of the collection system helps to ensure proper additive components and concentrations, controlled blood fill volume, correct blood/additive ratios, and sterilization. The presence of a gel separator to reduce the aliquot step decreases the risk of mislabeling and contamination. The gel may also increase specimen stability as compared to blood collection in nongel, nonaliquoted samples. However, without adequate training on proper phlebotomy technique and identification of sources of preanalytical error, changing collection devices alone is unlikely to deliver significant quality improvement. Therefore, a combination of training and incorporation of a closed collection system is recommended to aid in error reduction.

A multi-center study was performed in Mumbai, India to compare the incidence of preanalytical compromises using either a needle/syringe blood collection system and transferred to either a Vacutainer tube (BD Diagnostics, Franklin Lakes, NJ) or glass vial (traditional practice for these institutions) or using a closed collection system after phlebotomists' training in preanalytical science. Following collection of 19,081 samples, specimens were evaluated for a selection of criteria including inappropriate transport temperature, contamination of the sample, order of draw, inadequate separation of serum from clot, and the presence of hemolysis (*Table IV*) (6). The study concluded that while the use of the closed collection system did reduce the incidence of hemolysis, optimal results were achieved with a closed collection system combined with phlebotomy training.

Table IV Total incidence of hemolysis.

	Number of Samples Collected	Number of Hemolyzed Specimens	Percentage of Hemolyzed Specimens
BD Vacutainer Closed Collection System	10.955	7	0.06%
Syringe Needle Collection	8.126	1354	17%
Total	19.081	1361	7%

Serum Versus Plasma for TAT Reduction

Strategies can be implemented in the preanalytical phase to match the quality improvements in the analytical process. Rapid turnaround time (TAT) remains a key for healthcare facilities, particularly in the Emergency Department. One effective means to reduce TAT for clinical chemistry results is the use of heparin plasma specimens in lieu of serum (*Table V*). This eliminates the clotting time component (typically 30 minutes).

Table V Advantages and disadvantages of serum and plasma.

Advantages	Disadvantages
Serum: Nearly cell-free Good storage stability for most analytes Wide range of assays available	*Serum:* May cause pseudohyperkalemia, especially in patients with thrombocytosis Longer turnaround time Instrument or test interference from fibrin, particularly with anticoagulation therapy
Plasma: Shorter turnaround time; can be centrifuged immediately More representative of *in vivo* state Available plasma yield 15–20% higher than serum	*Plasma:* Higher cell/platelet counts; increased potential for testing errors with certain tests/instruments Reduced storage stability for certain analytes (especially in gel tubes); fibrin formation during storage Interference from anticoagulant and from fibrinogen Some tests may not be supported

Leaning Toward Cost Efficiency

Lean and Six Sigma methodology can be implemented to reduce preanalytical variability and to drive the standardization and integration of clinical processes. Adopted in the automotive industry, Lean technology emphasizes the elimination of waste as a means of streamlining operations, while Six Sigma removes variation to enhance performance (7).

How can these techniques be applied to the clinical laboratory? Simply, by incorporating these processes, laboratory professionals can focus on process performance by:

- Recognizing wasteful activities
- Reducing variation for more consistent production
- Error-proofing operations (as mistakes consume time and money)
- Assessing the preanalytical system as a whole rather than in parts in order to gain maximum improvement.

Improvement Through Education

An educational solution that includes specimen quality audits can be developed. This begins with an initial assessment of specimen collection practices, including a quantification of specimen rejection rates. This evaluation provides the laboratory team with the means to identify problem areas and to determine those areas that require attention, with the goal to sustain specimen quality and improve safety measures. In addition, targeted educational activities such as BD Prime (Preanalytical Improvement Through Education) can help to train staff in order to optimize the preanalytical phase.

Next, a follow up should be performed to ascertain the improvement in specimen collection practices and reduction in specimen rejection rates; finally, this process should be continuous to deter recurrence of previously inefficient laboratory practices.

Conclusion

Advancements in analytical performance have placed additional emphasis on quality improvement in the preanalytical phase. In addition, demands for cost reduction and more rapid turnaround time in the laboratory have reinforced the need for improved specimen quality and safety compliance. New approaches to preanalytical education in addition to Lean and Six Sigma methodologies have emerged as valuable tools to improve specimen quality and subsequently patient care.

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