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LABORATORY TESTING AND PREANALYTICAL ERRORS: WHERE ARE WE IN 2022?

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Abstract. *Inaccurate results of laboratory testing are mostly caused by errors in the preanalytical phase. The aim of this retrospective study is monitoring, documenting and preventing errors in the pre-analytical phase in order to provide better health care for patients. The study has been done from 2017 to 2021 and involves monitoring, documenting and preventing errors with aspect to phlebotomy in clinical biochemical laboratory of primary health care, in Students Health Protection Institute. Errors are classified in accordance with IFCC recommendation as quality indicators: insufficient sample volume, inappropriately labeled sample and sample damage. The study has shown that the most common errors are insufficient sample volume and sample damage (0.97 %). Inappropriately labeled samples were significantly lower and completely eliminated during period of study (2017 was 0.34 %, 2021 was 0 %; p<0.01). No significant decrease in number of sample damage (2017- 0.50 % - 2021- 0.30 %) was shown and insufficient sample volume errors (2017- 0.43% - 2021-0.32%) were constantly persisting during the period of study. Through permanent improvement and application of quality management system (QMS), implementation of certification and accreditation of laboratories according to the ISO15189, 2018- (QM / QA) standards for medical laboratories the entire laboratory testing process can be improved. Implementation of LIS (Laboratory Information System), the standard for POCT-ISO22870: 2006 Point of care testing, along with clear transparent and available procedures, errors in the pre-analytical phase can be minimized. Special attention should be paid on errors that continue to exist in the study. With more accurate, precise and valid results, correct and fast diagnosis, satisfied patients can be achieved with a smaller number of errors in pre-analytical phase and the principle of cost benefit can be achieved following the guideline: "no blood sample is better than a bad blood sample".*

Keywords: *Accreditation, laboratory testing, GLP, preanalytical errors, health care, patients*

1. INTRODUCTION

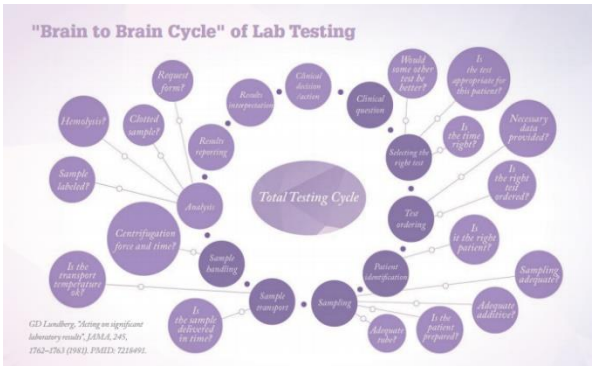
Survival of an organization, its success and labor are all dependent on quality. The role of the laboratory is to provide the highest quality service and to achieve the highest possible standards of professional and technical competence. Laboratories need to implement a number of complex technical procedures in order to determine parameters in biological/analytical sample necessary for the purpose of: diagnosis, monitoring the course of the disease and therapies and thus the creation of information with clinical expertise of the laboratory findings. The entire laboratory process should be:

- Defined
- Standardized
- Controlled and accredited.

In the overall health system in terms of diagnosis and treatment of patients only one small laboratory mistake can have significant repercussions as well as a financial impact.

In medicine, 70-85% of clinical decisions are based on knowledge derived from laboratory results; however, in various healthcare institutions laboratories are only given 3-5% of the annual budget [1].

"Brain to brain cycle" of lab testing enables that the right people while respecting the patient's opinion do the right things in the right order, time and place with good results. In laboratory medicine and diagnostics important indicators of quality are: TAT - turnaround time, IQA (Internal Quality Assessment), EQA (External Quality Assessment) as well as the number of errors, and the absence of objection. Laboratory medicine and clinical chemistry are complex interrelated disciplines that take place in three well-defined phases of the total laboratory process: preanalytical phase, analytical phase, postanalytical phase. Simultaneously quality assessment happens on three levels: technical level (analytical results), biological level (results), nosological level (Interpretation of results and interpretative comments on report) [3].



Picture 1. "Brain to brain cycle" of Lab Testing-Quality Realization

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Actions of various biological and interference factors can be reduced with standardization of conditions under the principles of good clinical practice (GCP), good laboratory practice (GLP) and monitoring according to evidence-based medicine (EBM). Errors in preanalytical phase can bring forth inaccurate results of laboratory testing.

Sources of errors in the preanalytical phase are inadequate preparation of patients, inexperience and a lack of skill of medical phlebotomists. Knowledge and prevention of factors that may occur in any of the 3 phases of the laboratory cycle is the key to valid results.

Tests have shown that in the pre-analytical phase of laboratory work; more than 2/3 of laboratory errors occur [4-8].

Picture 2. Clinical laboratories phases and errors
(Mario Plebani, Clin Chem Lab Med 2006)

Laboratory errors of total testing process

Pre-preanalytical phase – type of error
- ✓ Wrong clinical question
- ✓ Wrong test selection-surplus/deficiency
- ✓ Misguided preparation of the patient (communication, lack of written information)
- ✓ Non-compliance with biological variables
- ✓ Misspelled instructions-incomplete data

"Misidentification" causes
- ✓ Selected tests for the wrong patient
- ✓ LIS data with incorrect or incomplete patient documentation
- ✓ Blood sampling from the wrong patient
- ✓ Inadequate labels
- ✓ Lost sample labels
- ✓ Wrong entry for patient in LIS

Preanalytical phase – type of errors
- ✓ Misidentification of patient, samples
- ✓ LIS input errors, manual input errors
- ✓ Mishandled sampling procedure
- ✓ Wrong selection of test tubes and other disposable materials
- ✓ Wrong ratio of blood/anticoagulants-reduced
- ✓ Increased blood volume
- ✓ Blood extracted from the infusion site
- ✓ Patient injuries, gloves, blunts, blindfolds
- ✓ Mislabeled test tubes
- ✓ Incorrect sample transport
- ✓ Incorrect centrifuge
- ✓ Incorrect sorting, processing in analytical work
- ✓ Serum outflow errors, marking glasses
- ✓ Exposure to biohazards

Analytical phase – type of error
- ✓ Non-compliance with procedures
- ✓ Sample Preparation Errors
- ✓ Test-Calibration Analyzer
- ✓ (Technical problems)
- ✓ Internal and external control error
- ✓ Sample Substitution
- ✓ Impact of interference
- ✓ Verify results in LIS

Postnalytical phase – type of error
- ✓ Misvalidation of results
- ✓ Misplaced/Inscribed Results in LIS/Manual
- ✓ Mis/relabeled Results
- ✓ Reference values, cut off values
- ✓ Non-report critical values (not logging)
- ✓ Non-compliance with urgent requests
- ✓ Incorrect storing and keeping of samples
- ✓ Exceeded TAT
- ✓ Wrong comment/lack of comment

Post-Postnalytical phase – type of error
- ✓ Interpretation of laboratory results
- ✓ Clinical interpretation of results
- ✓ Making a clinical decision (further referral, treatment plan) [9-12].

Laboratory specialists and staff with their clinical experience are able to identify incoherent results when comparing them to previous results or to other parameters and prevent some preanalytical errors. Clinical expertise can be done between thyroid stimulating hormone (TSH) and free thyroxine (FT4) and/or free triiodothyronine (FT3) in thyroid diseases, alkaline phosphatase (ALP), calcium and 25-hydroxyvitamin D (VitD) in bone metabolism and joint diseases; androstenedione, dehydroepiandrosterone sulfate (DHEA-S) and testosterone in endocrine diseases; cardiac troponin (cTn), creatinine-kinase (CK), CK-myocardial band (CK-MB) in acute myocardial infarction and cardiovascular diseases [1,24].

Algorithms important for suspicion of biological interferences consist of the following parameters: reference intervals of parameters in context of age and sex, interpretations in context of medication, fasted state, posture (levels of renin), physical activity with increase in D-dimers, N-terminal pro-brain natriuretic peptide (NT-proBNP), cTn in elite athletes [11], circadian cycle with increase of cortisol, adrenocorticotropic hormone (ACTH), testosterone, TSH, stress with changes of prolactin (PRL), growth hormone (GH), thyroid hormones [13].

The most often discovered errors in laboratories are preanalytical errors [8]. Those errors fit in four categories: (a) sampling errors with problems of venous stasis, order of blood tube draws, anticoagulant type, tube filling and homogenization, (b) identification errors (c) transportation errors (changes in stability, temperature), (d) preparation errors like centrifugation and aliquoting [2]. Incorrect sample identification, invalid tube filling, inadequate choice of tubes, clotted samples, inaccurate analysis request forms, faulty transportation and conservation and *in vitro* hemolysis are the most important preanalytical errors [9]. We must pay attention to the following: identification of the patient should be inspected and confirmed with tube integrity, (additives) [14] tube type and filling, clotting should be verified in agreement with good laboratory

practices [10]. The adequate filling of the tube is very important for analyses measured in tubes with citrate as an anticoagulant (D-dimers) and should be respected to avoid falsely negative results, especially nowadays with the covid pandemic [15]. However, most biochemical parameters are stable at room temperature (RT) for several hours and only a few of them are sensitive to transportation conditions. Assay ACTH needs to be done with tube using ethylenediamine tetraacetic acid (EDTA) as an anticoagulant because a calcium chelator limits enzymatic degradation [16]. In some assays, EDTA and citrate may interfere through chelation of europium labels [17]. In hormone biochemical quantitative analysis, lithium heparin tubes are generally accepted [18], [19]. Fibrin may also cause interferences when generated from residual fibrinogen in case of inadequate post-phlebotomy tube homogenization [21]. Stability of various parameters is very sensitive to inadequate mixing and can also lead to decreased values [14]. The majorities of biological parameters determining serum samples on the other hand are not affected by anticoagulants and exhibit a good stability [17]. Tubes needs a clotting phase of about 30 min to an hour before centrifugation to eliminate fibrinogen, fibrin and blood cells which may interfere with the clinical-biochemical analysis and for these reasons prolonging the global TAT [18]. Parathyroid hormone (PTH) degenerates faster in serum than in EDTA [20]. Renin, glucagon, and gastrin are also fragile and problematic parameters [22]. The analysis of some parameters such as phenobarbital, phenytoin, and carbamazepine can be influenced in a few hours by the use of separating gel. Progesterone may adsorb separating gel in a few days if left in tubes [26]. Parameter stability finally can be influenced by fundamental elements such as time of collection and transportation conditions from collecting point to the laboratory [28]. A new sample is required and should be monitored to ensure a valid analysis if a preanalytical error is recognized earlier before the analytical phase [27]. Analytical errors are generally classified as exogenous and endogenous errors [22]. Exogenous errors are associated to analytical procedure accidents such as calibration or reagent degradation, imprecise pipetting or washing issues. Adequate quality monitoring by checking results from internal (IQC) and external quality controls (EQC) can filter out these errors through a careful analysis of automatically issued messages from the analyzer. Two types of endogenous errors are: type 1 endogenous errors like hemolysis, icteria, lipemia (HIL) and these can be detected before the analytical phase and type 2 endogenous errors like influences and interferences of heterophilic antibodies, biotin, autoantibodies and these are hard to detect during the preanalytical phase [1]. Last-mentioned are errors not detected by a comprehensive impact of IQC/EQC [29]. Modern analyzers use spectrophotometric measures to better recognize type 1 endogenous errors, even if immunoassays, radio assays are generally less affected in comparison to photometric assays [19]. Suitable break points can be applied to detect lipemia interference and different methods can be followed in order to overcome the erroneous result. Laboratory medicine using ultracentrifugation, high-speed centrifugation, and lipid-clearing agents can avoid these problems [25]. New samples are required if type 1 endogenous errors cannot be eliminated.

2. Materials and methods

In the clinical biochemical laboratory of primary health care in Students Health Protection Institute of the University of Novi Sad, Serbia from 2017 to 2021 a retrospective study has been done which involves monitoring, documenting and preventing errors with aspect to phlebotomy for better health care of students. Errors are classified in accordance to IFCC recommendation as quality indicators: insufficient sample volume, inappropriately labeled sample and sample damage.

3. Results

Results of study have shown that the most common errors are insufficient sample volume and sample damage (0.97 %).

During the period of study, inappropriately labeled samples were significantly lower and completely eliminated, as can be seen in Figure 1 (2017 was 0.34 %, 2021 was 0 %; p<0. 01).

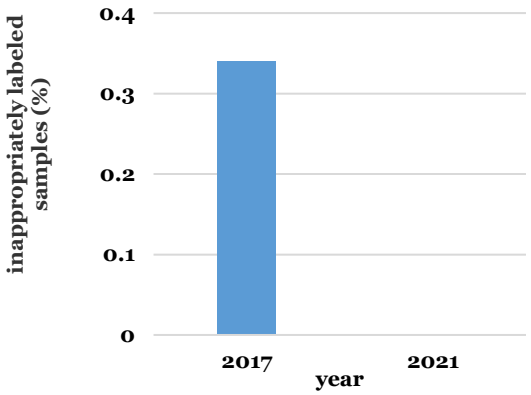

Figure 1. Clinical data results – inappropriately labeled samples

Number of samples damaged during the period of study showed no significant decrease (2017- 0.50 % - 2021- 0.30 %) shown in Figure 2.

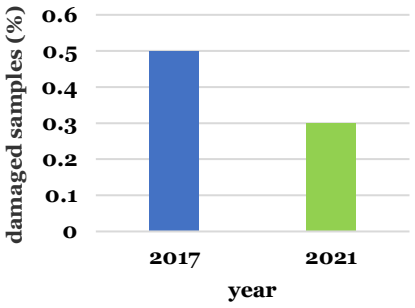

Figure 2. Clinical data results -damaged samples

During the period of study, insufficient sample volume errors (2017-0.43% – 2021-0.32%) were constantly persisting and these are shown in Figure 3.

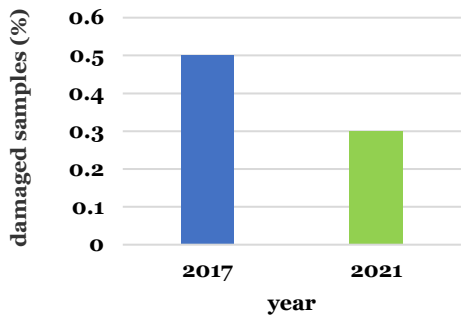

Figure 3. Clinical data results -insufficient sample volume

4. Discussion

We can reduce preanalytical errors by quality control, identification and follow-up of possible causes of preanalytical errors. QA programs must include monitoring of sample collection, good medical practice, knowledge of GLP vs. hospital procedures and the best medical practice according to EBM, have educational and training programs, support staff in efficient CME, quality laboratory products, and don't forget quality vacuum systems and needles. The vacuum system is the primary most important element that connects each phase in the laboratory. Laboratories should take care about taking samples as they are analyzers or reagents [23]. Pre-analytic problems are source of post-analytical errors. Preanalytical errors have effects like:

- Incorrectly marked sample
- Hemolyzed sample
- Insufficient sample amount
- Inadequate use of vacuum system
- Coagulated sample and their resulting in:

- Wrong Diagnosis
- Unnecessary surgical interventions
- Patient mistrust
- Violated reputation
- Financial loss

Standardization, education and automation are the necessary steps to an improved preanalytical phase and require continuous funding. Education must be continually monitored, and on its own is not enough because laboratory workers must have experiences also. With use of targeted laboratory diagnostics, it is possible to achieve significant material savings [6, 9, 22, 23].

Measures for enhancing the quality of health services rely on basic components and factors of quality such as: personnel, education and training of employees, dependence on adequate equipment, innovation of services, quality and standardization of performed services through the application of QMS [1-8].

Accreditation suggests: fulfillment of the quality management system and fulfillment of technical requirements, the competence for all laboratory tasks (the testing methods are appropriated) according to the ISO 15189 and POCT-ISO22870 standard. ISO15189:2018- (QM / QA) is standard for medical laboratories with a special requirement for quality and competence of the entire laboratory testing – pre-analytical, analytical and post-analytical work process). Standard POCT-ISO22870:2006 represent requirements for quality and competence for point of cares testing, ISO/TS 22367:2008 are for laboratory errors in TTC. Significance of accreditation is in improvement of organization services, fulfilling customer service requests, recognition of competence and improving leadership and management [6, 20, and 22].

5. Conclusion and future directions

Specific goals for health policy of total testing laboratory process -TTLP in laboratory medicine are in the next few steps: improving the capacities of human resources, certification of methods, procedures and accreditation of laboratories, implementation of external and internal quality control, rational application of laboratory diagnostics, rational use of health technologies, developing guidelines for good laboratory practice. The following is needed: clear definition of responsibilities, transparent and available communication with phlebotomists, well defined procedures/processes that are written in the workplace, permanently improvement of the QMS, implementation of certification and accreditation of laboratories (QM / QA), and implementation of LIS (Laboratory Information System). Automating functions has led to the biggest reduction in pre-analytical phase errors. Special attention should be paid on errors that continue to exist in the study in future scientific papers.

In conclusion, a smaller number of errors in pre-analytical phase mean more accurate, precise and valid results, accurate and fast diagnosis, satisfied patients and principle of cost benefit with guideline: "no blood sample is better than a bad blood sample".

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