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Review article
Pregledni članak

PRE-ANALYTICAL ERRORS AND PATIENT SAFETY

PREANALITIČKE GREŠKE I BEZBEDNOST PACIJENATA

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Summary: Laboratory medicine, as a specialty that had prioritised quality control, has always been at the forefront of error reduction. In the last decades, a dramatic decrease of analytical errors has been experienced, while a relatively high frequency of errors has been documented in the pre-analytical phase. Most pre-analytical errors, which account for up to 70% of all mistakes made in laboratory diagnostics, arise during patient preparation, and sample collection, transportation, preparation for analysis and storage. However, while it has been reported that the pre-analytical phase is error-prone, only recently has it been demonstrated that most of these errors occur in the »pre-pre-analytical phase«, which comprises the initial procedures of the testing process performed outside the laboratory walls by healthcare personnel outside the direct control of the clinical laboratory. Developments in automation and information technologies have played a major role in decreasing some pre-analytical errors and, in particular, the automation of repetitive, error-prone and bio-hazardous pre-analytical processes performed within the laboratory walls has effectively decreased errors in specimen preparation, centrifugation, aliquot preparation, pipetting and sorting. However, more efforts should be made to improve the appropriateness of test request, patient and sample identification procedures and other pre-analytical steps performed outside the laboratory walls.

Keywords: quality indicators, errors in laboratory medicine, pre-analytical phase, pre-pre-analytical phase, total testing process, quality specifications

Kratak sadr`aj: Laboratorijska medicina, kao specijalnost u kojoj je prioritet kontrola kvaliteta, uvek je prednjačila u redukciji grešaka. U prošloj deceniji došlo je do dramatičnog smanjenja broja analitičkih grešaka, dok je relativno visoka učestalost grešaka zabeležena u preanalitičkoj fazi. Preanalitičke greške, koje čine i do 70% ukupnog broja grešaka u laboratorijskoj dijagnostici, većinom nastaju tokom pripreme pacijenta i sakupljanja uzoraka, njihovog transporta, pripreme za analizu i skladištenja. Međutim, mada je ustanovljeno da je preanalitička faza podložna greškama, tek nedavno je pokazano da većina tih grešaka nastaje u »pre-preanalitičkoj fazi«, koja obuhvata početne postupke u procesu testiranja koje izvan zidova laboratorije izvode zdravstveni radnici koji nisu pod direktnom kontrolom kliničke laboratorije. Razvoj automatizacije i informacionih tehnologija presudno je uticao na smanjenje broja nekih preanalitičkih grešaka, a naročito je automatizacija preanalitičkih postupaka podložnih greškama koji se izvode u okviru laboratorije efikasno snizila broj grešaka u pripremi uzoraka, centrifugiranju, pripremi alikvota, pipetiranju i sortiranju. Ipak, potrebni su dodatni napori kako bi se postiglo da zahtevi za testovima budu potpuno odgovarajući i da bi se unapredili postupci identifikacije pacijenta i uzorka kao i ostali preanalitički koraci koji se izvode izvan laboratorije.

Ključne reči: indikatori kvaliteta, greške u laboratorijskoj medicini, preanalitička faza, pre-preanalitička faza, ukupni proces testiranja, specifikacije kvaliteta

Introduction

Laboratory medicine has a long history of careful attention to quality assurance, standard setting and performance monitoring. This is an important foundation to built upon for reducing the risk of errors and improving patient safety. Quality in laboratory medicine should be defined as the guarantee that each and every step in the »brain-to-brain turnaround time loop« is correctly performed, thus assuring a

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valuable medical decision making process and effective patient care. As stated several years ago by Lundberg (1, 2), the generation of any laboratory test result involves nine steps: ordering, collection, identification, transportation, separation or preparation, analysis, reporting, and action. Changes made to the medical landscape have greatly impacted on the delivery of laboratory services, but although the »brain-to-brain« concept was described as long as 40 years ago, it is still considered the working paradigm in assuring quality and safety to requesting physicians and patients (3). In particular, the »brain-to-brain« concept strongly supports the moving from a »laboratory-centered« scenario which recognised only analytical errors, to a »patient-centered« scenario that focus on errors in the total testing process.

In the past decades, a ten-fold reduction has been achieved in the analytical error rates (4) thanks to improvements in the reliability and standardization of analytic techniques, reagents, instrumentations and advancements in information technology as well as in quality control and assurance methods. According to recent evidence, most errors in the loop fall outside the analytical phase, while pre- and post-analytical steps have been found to be more vulnerable to the risk of error (5, 6). In particular, a body of evidence has been collected to demonstrate that pre-analytical steps are error-prone and that errors in these steps present a high risk for patient safety.

Errors in the pre-analytical phase

Currently, pre-analytical errors account for up to 70% of all mistakes made in laboratory diagnostics, most of which arise from problems in patient preparation, and sample collection, transportation, preparation for analysis and storage (7). Although most of these errors would be »intercepted« by laboratory professionals or physicians before inappropriate actions are taken on the patient based on these unreliable results, in nearly one-fifth of the cases these errors might be associated with further inappropriate investigations and unjustifiable increase in costs (4). According to the ISO 15189: 2007 International Standard for laboratory accreditation, the pre-analytical phase should be defined as »steps starting, in chronological order, from the clinician's request and including the examination requisition, preparation of the patient, collection of the primary sample, and transportation to and within the laboratory, and ending when the analytical examination procedure begins« (8). This definition clearly recognizes the need to evaluate, monitor and improve all the procedures and processes in the initial phase of laboratory testing, not only the procedures performed within the laboratory walls.

In fact, the pre-analytical phase should be subdivided into a »pre-pre-analytical phase« and a »true« pre-analytical phase, which is undertaken within the laboratory walls after specimen reception. The former phase, which comprises initial procedures usually performed neither in the clinical laboratory nor undertaken, at least in part, under the control of laboratory personnel, includes test requesting, patient and sample identification and sample collection. The latter involves the steps required to prepare samples for analysis (centrifugation, aliquoting, and sorting). *Table I* shows the most frequent pre-analytical errors (7).

Table I Most frequent pre-pre-analytical errors

1. Missing sample and/or test request
2. Wrong/missing identification
3. In vitro haemolysis
4. Undue clotting
5. Wrong container
6. Contamination from infusion route
7. Insufficient sample
8. Inappropriate blood to anticoagulant ratio
9. Insufficient mixing of the sample
10. Inappropriate transport and storage conditions

It is easy to recognize that most of the errors listed in *Table I* arise from procedures performed outside the laboratory walls by healthcare personnel (physicians and nurses) who usually are not under the direct control of the laboratory. This finding, in addition, clearly explains previously reported data on the different pre-analytical error rates detected in some laboratory institutions when comparing in-patient and out-patients samples. In fact, the rates of pre-analytic errors were found to be higher for in-patients than outpatients, for whom procedures are performed by personnel under direct laboratory control (9).

Errors in the »pre-pre-analytical phase«

The nature of pre-analytical errors has to be better evaluated through the exploration at the beginning of the loop, the initial steps of the cycle that have been grouped into the so-called »pre-pre-analytical phase«. These activities, that were poorly evaluated and monitored, often because the process owner is unidentified and the responsibility falls in the boundaries between laboratory and clinical departments, present a high risk of errors and, even more important, errors which may compromise patient safety. In a recently published paper, we have evaluated the pre-analytical errors detected in the clinical laboratory in relationship with the procedures and processes performed in three wards (10). The frequency of errors was found to be very high in the pre-pre-ana-

lytic (namely order transmission, at 29,916 parts per million, ppm) and in the pre-analytic steps, being particularly high for hemolyzed samples (2586 ppm), incorrect sample delivery (1170 ppm), clotted (887 ppm) and underfilled sample tubes (622 ppm). The frequency of patient misidentification was 359 ppm. The most frequent non-conformities were found to be test request recorded in the diary without the patient's name being entered, only the bed number being specified, and failure to check the patient's identity on the appropriate wristband at the time of blood drawing. Therefore, this study demonstrated that most pre-analytical errors are related to the lack of compliance by healthcare personnel (physicians and nurses) with the existing standard operating procedures for blood collection and patient identification. The main »take home message« is the need to consensually (between the laboratory and the wards) prepare and adopt standard operating procedures for safely performing patient identification and preparation, test requesting and blood collection.

For example, it is well known that haemolysis is the leading cause of unsuitable specimens, and the release of recommendations for the management of haemolysed samples (11) as well as the adoption of the haemolysis index, an automated and objective mean for identifying haemolysis in clinical practice, represented formidable tools for an »evidence-based« management of patient samples (12). However, an effective reduction of haemolysed samples should be achieved only through a better training and education of healthcare operators other than laboratorians.

Test Request

While the problem of inappropriate test request has been reported a long time ago, recent data demonstrate that physicians face a major challenge in selecting the correct tests due to the increased number and complexity of laboratory tests and inadequate training at the medical schools. Attempts to improve testing by feedback, education, and computerized aid have been reported with conflicting results (13). Laposata and colleagues have used and reported a strategy that combines the search for efficiency, including cost reduction, and effectiveness linking together improvements in the pre-pre- and post-post-analytic phases. Briefly, they ask the requesting clinicians to substitute the request of individual coagulation tests with the clinical question or diagnostic suspicion. According to this strategy the clinical laboratory performs some »simple« initial tests and, on the basis of these preliminary results, may conclude the diagnostic path, or may select further and appropriate tests through the use of diagnostic algorithms and reflex testing. The final step of the process is the addition to the laboratory report of interpretative comments, the so-called »narrative interpretations« that have proven to shorten the time to diagnosis, and improve its accuracy, while reducing the number of tests (14). Laposata et al. (15) demonstrated the usefulness of this »narrative interpretation service« in order to improve diagnostic accuracy while saving time and reducing cost of care not only in coagulation but also in autoimmune, haematological, and endocrinological diseases. Many recently published papers from the clinical side have recognized the relatively high frequency of inappropriate test request and the associated clinical risk, thus stressing the need for further initiatives in this area.

Errors in the »true pre-analytical« phase

According to the previously described recognition and definition of the »pre-pre-analytical phase«, true pre-analytical errors should be considered only those performed within the laboratory walls, in steps required for accepting and preparing biological samples to be analyzed. Thanks to the introduction of pre-analytic workstations, a significant reduction has been achieved in pre-analytic errors. In fact, regardless of the different approaches (standalone or integrated workstations), all these pre-analytical solutions have

Table II Technological, informatic and computer science advances in the pre-analytical phase (from Reference 6, modified).

- Computerized physician order entry (CPOE)
- Positive patient identification by
  - Barcode technology
  - Smart cards
  - Radio-frequency identification (RFID)
  - Optical character recognition and voice recognition devices
- »Active tubes« (lab-on-a-chip integrated containers)
  Storage of patient data, measurement of physiological (e.g., temperature/humidity/flow rate) and metabolic data (e.g., glucose concentration)
- Transport systems
  - Pneumatic tubes conveyer
  - Robots
  - Transportation monitoring systems (e.g., time of transportation, temperature, humidity, etc.)
- Instrumentation tools
  - Query-host communication
  - Primary tube processing
  - Volume/clotting/bubbles sensors
  - Serum indices
- Informatics tools
  - Query-host communication
  - Automatic validation
  - Expert systems
  - Delta check technology
  - Error-recording software

the potential to automatically inspect, bar code, centrifuge, decap, sort, check sample volume and detect clot in patient samples (16). In addition, they may create aliquots and apply secondary tube labeling, sorting into analyzer racks, and eventually storing the specimens, thus reducing the risk of errors due to manually performed procedures. *Table II* shows the most important technological developments introduced in clinical laboratories to improve the quality of the pre-analytical phase.

Quality in sample transportation

Sample transportation is widely recognized as a major factor contributing to delays in returning high-quality clinical laboratory results to both the patient's bedside and to outpatients. In the last few years, findings have been collected concerning the effects of extreme temperatures and physical forces during sample transportation via pneumatic systems (PTS) (17, 18). In particular, it has been demonstrated that PTS speed affects the degree of hemolysis (19, 20). Yet little attention has been paid to the effects of sample transportation from peripheral collection sites to centralized laboratory facilities. In the last few decades, due to increasing pressure to cut costs in healthcare organizations, we have experienced the increasing consolidation and centralization of laboratory diagnostics within large facilities, with a consequent need to transport a large number of specimens from peripheral collection sites to the core laboratories; this has led to a dramatic increase in the risk of errors in this step, and the urgent need for appropriate sample transportation conditions. We have recently published two papers dealing with quality in sample transportation. In particular, in the first paper, we confirmed the usefulness of an integrated system (secondary and tertiary containers, data logger and system manager) that allows effective monitoring of the transportation time and temperature of biological samples throughout transportation from collecting centers to the laboratory (21). In the second paper, we demonstrated the effects of the integrated system for sample transportation on the quality of six commonly requested laboratory tests, selected on the basis of the possible interference of time and temperature on their measured concentration. For three parameters (K, ALT and APTT), significant differences due to transportation time have been observed before the introduction of the integrated system (22). In particular, considering samples with a transportation time of less than one hour and those with transportation times of more than one and a half hours, the concentrations of the two common laboratory tests ALT and K were different. Therefore both studies confirmed the need to standardize time and temperature conditions during sample transportation by adopting integrated systems that obviate possible interferences and poor pre-analytical quality.

Quality indicators in the pre-analytic phase

According to the approach of the Institute of Medicine (IOM) to quality in healthcare, the identification of reliable quality indicators (QIs) is a crucial step in enabling users to quantify the quality of a selected aspect of care by comparing it against a

Table III Quality indicators in the pre-analytic phase

QI-1: Appropriateness of test request.	Number of requests with clinical question (%)
QI-2: Appropriateness of test request.	Number of appropriate tests with respect to the clinical question (%)
QI-3: Examination requisition	Number of requests without physician's identification (%)
QI-4: Examination requisition	Number of unintelligible requests (%)
QI-5: Identification	Number of requests with erroneous patient identification (%)
QI-6: Identification	Number of requests with erroneous identification of physician
QI-7: Test request	Number of requests with errors concerning test input (%)
QI-8: Samples	Number of samples lost/not received (%)
QI-9: Samples	Number of samples collected in inappropriate containers (%)
QI-10: Samples	Number of samples haemolysed (haematology, chemistry)
QI-11: Samples	Number of samples clotted (haematology, chemistry)
QI-12: Samples	Number of samples in insufficient volumes (%)
QI-13: Samples	Number of samples with inadequate sample – anticoagulant ratio (%)
QI-14: Samples	Number of samples damaged in transport (%)
QI-15: Samples	Number of improperly labelled samples (%)
QI-16: Samples	Number of improperly stored samples (%)

defined criterion (23). A quality indicator is thus »an objective measure that potentially evaluates all critical care domains as defined by the IOM (patient safety , effectiveness, equity, patient-centeredness, timeliness and efficiency), (that) is based on evidence associated with those domains, and can be implemented in a consistent and comparable manner acr oss settings and over time« (24). In a patient-centr ed scenario, quality indicators should be designed to cover all steps of the pre-analytical phase, from test requesting to sample storage.

The 16 QIs developed by the IFCC -WG for the pre-analytic phase (25) are shown in *Table III*.

Preliminary data collected by several laboratories worldwide underlined the importance of quality indicators to provide evidence regarding the quality of laboratory processes, namely in the pr e-analytical phase (26). However, further data should be collected from a higher number of clinical laboratories to provide reliable quality specifications for each indicator. This in tur n may allow clinical laboratories to implement quality impr ovement initiatives based on objective data.

Conclusions

In the last decades, a dramatic decrease of analytical errors has been experienced, while a r elatively high frequency of errors has been documented in the pre-analytical phase. Most pre-analytical errors, which account for up to 70% of all mistakes made in laboratory diagnostics, arise during patient pr eparation, and sample collection, transportation, preparation for analysis and storage (27). The development of quality indicators in laborator y medicine is a fundamental step in providing sound evidence of quality in all pr ocedures and processes of the total testing pr ocess in accreditation programs as well as in ensuring that continuous improvement activities aiming to r educe the risk of er rors in clinical practice ar e undertaken. However, particularly for QIs in the pr e-analytical phase, which investigate pr ocedures that ar e usually performed by healthcar e operators outside the laboratory walls, collecting data on QIs and monitoring them does not automatically result in quality improvement (28). Effective improvements in the initial (and final) steps of the TTP can be achieved only if further efforts are made to achieve consensus on the pr eparation, adoption and monitoring of effective standar d operating procedures in the initial steps of laborator y testing (10).

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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