Abstract

Clinical laboratories play an important role in improving patient care. The past decades have seen unbelievable, often unpredictable improvements in analytical performance. Although the seminal concept of the brain-to-brain laboratory loop has been described more than four decades ago, there is now a growing awareness about the importance of extra-analytical aspects in laboratory quality. According to this concept, all phases and activities of the testing cycle should be assessed, monitored and improved in order to decrease the total error rates thereby improving patients’ safety. Clinical Chemistry and Laboratory Medicine (CCLM) not only has followed the shift in perception of quality in the discipline, but has been the catalyst for promoting a large debate on this topic, underlining the value of papers dealing with errors in clinical laboratories and possible remedies, as well as new approaches to the definition of quality in pre-, intra-, and post-analytical steps. The celebration of the 50th anniversary of the CCLM journal offers the opportunity to recall and mention some milestones in the approach to quality and patient safety and to inform our readers, as well as laboratory professionals, clinicians and all the stakeholders of the willingness of the journal to maintain quality issues as central to its interest even in the future.

Keywords: brain-to-brain loop; Clinical Chemistry and Laboratory Medicine; laboratory errors; laboratory medicine; patient safety; quality.

Introduction

Laboratory medicine, along with other healthcare sectors, is widely recognized for the continuous development of new models for quality which, on closer inspection, turn out to be rather similar to the old initiatives and only differ for a new label. Is it “patient safety” a new bottle for an old wine? Some of the core ideas and concepts of patient safety could certainly be identified in the earlier writing from the quality pioneers and leaders, although seldom in rather embryonic form [1]. Focusing on laboratory medicine, it should be underlined that a seminal editorial published in 1998 by George D. Lundberg, the inventor of the “brain-to-brain” concept, emphasized the importance to “be concerned about the effects of a laboratory tests and whether the performance of it was useful for the patient or for the public health”, thus stressing the need for an outcome research agenda [2]. Patient safety has been, at the simplest, defined as “the avoidance, prevention and amelioration of adverse outcomes or injuries stemming from the process of healthcare” [3]. Readdressing the issue of the value in healthcare, the need to measure the “value by the outcomes achieved, not the volumes of services delivered” was recently underlined [4]. Measuring, reporting, and comparing outcomes are, therefore, the most important steps towards a safer healthcare system. Although studies of outcomes related to the use of laboratory tests are inherently biased by several drawbacks, namely the remoteness of several potential outcomes from testing and the inconsistent medical response to laboratory results [5], these studies are becoming more common. Recently, Barth postulated that “over the past few years, there has been a paradigm shift in the delivery of laboratory medicine to a clinical service measured by outcomes” [6]. In fact, while studies on laboratory-related outcomes are complex because multiple steps occur between testing and outcomes and physicians act unpredictably, a wide consensus has been achieved on the need to evaluate not only the analytical accuracy of a diagnostic test, but also its diagnostic effectiveness through a
careful analysis of the balance between expected benefits and risks. It is well-known that any diagnostic procedure, including laboratory tests, carries some risks in terms of both direct harmfulness to patients, discomfort, anxiety and financial burden. According to the previously mentioned definition of “patient safety”, a focus on the risk of adverse outcomes related to laboratory testing and on their prevention represents a major challenge for laboratory medicine. Therefore, the focus on patient safety does not seem to be a new label for an ancient initiative, but the evolution of the efforts to demonstrate the effect of laboratory testing on patient outcomes. Here, we would like to review the issue of errors in laboratory medicine and related effects on patient safety, and the role of Clinical Chemistry and Laboratory Medicine (CCLM) in improving and spreading the knowledge on this topic.

Laboratory errors: is the analytic phase really safer?

Laboratory-associated error has a completely different meaning today than it did five decades ago. At that time, the term was used for defects in the analytical performance of the test, the so-called “analytic phase”. The seminal paper by Belk and Sunderman, which paved the way to the development of external quality assessment (EQA) programs focused almost exclusively on analytical errors, identified high rates and serious errors in the measurement of “simple” clinical chemistry analytes [7]. A comprehensive analysis of the data collected and reported in the literature, beginning with the previously mentioned paper through the results collected by the College of American Pathologists (CAP) in the 1990s, and finally the data published by Witte and coworkers in 1997, shows that the analytical error rates decreased remarkably from 162,116 per million laboratory tests (part per million, ppm) to 447 ppm [7–10]. This dramatic and impressive reduction (i.e., ∼300-fold), has principally emerged from the widespread introduction of automation, information technology, improved laboratory technology, assay standardization, well-defined rules for internal quality control (IQC), as well as effective quality assurance schemes and better training for the laboratory professionals. However, despite the impressive improvement achieved in analytical quality, several lines of evidence demonstrate that further improvements in this field are advisable. Data collected in the US demonstrates that analytical quality is still a major issue. Westgard has shown that estimates on σ scale for common clinical chemistry and coagulation tests are unsatisfactory, ranging from 3 to 4 σ, at best [11]. A relatively high frequency of analytical error has been reported for immunoassays, with associated adverse clinical outcomes. Interferences from heterophilic and anti-human antibodies still cause grossly erroneous results and adverse clinical outcomes [12–15]. Recently, data collected on the interference of paraproteins in several laboratory assays, including glucose, bilirubin, C-reactive protein, creatinine and albumin, demonstrate that the frequency of this type of error is variable and largely underreported [16, 17]. Unsatisfactory analytical performances have been described not only in the field of clinical chemistry, but also in hematology, coagulation, and molecular biology testing [11]. In particular, a lack of reproducibility has been reported for common manual tests, such as Gram stains [18], the ANCA test with perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibody results leading to misdiagnosis of Wegener’s granulomatosis and resulting in significant morbidity and mortality events [19]. Therefore, analytical quality has been improved over the past decades but further efforts still need to be made. As a matter of fact, evidence exists to demonstrate that clinical laboratories performances in external quality assessment/proficiency testing (EQA/PT) programs are not satisfactory and that more emphasis must be put on the search for standardization and harmonization of laboratory results [20]. A better analytical quality should be achieved by setting and implementing evidence-based analytical quality specifications in everyday practice; if this will be done, rules for internal quality control and external quality assessment procedures would be more appropriate. Moreover, there is a compelling need for standardization programs aimed at improving metrological traceability and correcting biases and systematic errors. Finally, more stringent metrics, such as the Six Sigma, should be largely introduced in clinical laboratories, to further improve current analytical quality.

Errors in the total testing process

The importance to errors in the total testing process was recognized many decades ago, but it was only in 1990s a body of evidence has been accumulated to demonstrate the high vulnerability of the pre- and post-analytic phases. In 1975 George D Lundberg coined the foremost concept of “brain-to-brain turnaround time” [21], and he better described the seminal concept of the “brain-to-brain loop” 6 years later. According to this concept, the generation of any laboratory test result consists of nine steps including ordering,
collection, identification (at several stages), transportation, separation (or preparation), analysis, reporting, interpretation and action [22]. Lundberg highlighted that “anything that stands in the way of their (physicians) prompt and perfect receiving of laboratory results for their patients is perceived as a laboratory problem or error” and that the responsibility of laboratory professionals cannot be limited to perform and monitor analytical quality. However, the evidence on the high rates of errors in the pre- and post-analytical has been slowly achieved, and it was only in the early 1990s that a series of studies catalyzed the attention of the laboratory professionals to extra-analytical activities. In particular, two important articles were published in 1997 and 2007 [23, 24], using one study design that allowed the assessment of most TTP steps within the same clinical context and thereby defined the utility and effectiveness of the interventions. The results obtained were substantially similar, demonstrating that the distribution of errors was 62%–68% pre-analytical, 13%–15% analytical, and 18%–23% post-analytical. The latter study, published 10 years after the former, demonstrated a significant, although not dramatic, decrease in the error rates and a similar distribution of errors. The pre-analytical phase showed the highest error rate, the most frequent problems due to mistakes in tube filling, use of inappropriate containers, and inaccurate requesting procedures. Identification errors occurred for three patients and 14 related tests (875 ppm) in the latter study, but were significantly fewer than those observed in the former for specimens collected from infusion routes. The main reason for errors in the post-analytical phase was an excessive turnaround time in the latter survey, and errors in keyboard entry and missed correction of erroneous findings in the former. Thanks to improvements in information technologies, a remarkable reduction has been achieved in test transcription and ward identification errors. However, new types of error have emerged, particularly those attributable to the staff’s application of novel information procedures. The laboratory community was initially refractory to accept these evidences that however should be clearly predictable since both the pre- and post-analytical phases pertain not only to the laboratory, and involve other health care operators in test ordering, data entry, specimen collection and handling. In particular, it has been underlined that the dictum “the evil is in the boundaries” aptly points to the problems related to the poor attention and/or quality of procedures and processes at the interface between laboratory and clinical practices [25].

The evidence that pre- and post-analytical activities are highly vulnerable, however, does not represent the end of the story but just its beginning. Further studies and publications have better elucidated the nature of errors in laboratory testing through two different but converging research lines. The first is the exploration of the initial and final steps of the testing process that have been grouped and defined “pre-pre-analytical” and “post-post-analytical”, respectively [25]. In particular, the exploration of the initial steps of the “procedures which are usually performed neither in the clinical laboratory, nor, at least in part, under the control of the laboratory personnel” [17], has allowed the understanding of the causes and the underlying mechanisms that produce most of pre-analytical errors [26]. Again, in the final steps of the loop, a delayed acknowledgment of laboratory reports, as well as failures in interpretation, follow-up and documentation of laboratory data were found to be responsible for a high percentage of errors in various clinical settings.

The second research path, which has started from the clinical side, demonstrated that errors in laboratory medicine represent a piece of a much wider puzzle that is commonly known as “diagnostic error”. The definition of diagnostic errors as “errors in which diagnosis was unintentionally delayed (while sufficient information was available earlier), wrong (another diagnosis was made before the correct one), or missed (no diagnosis was ever made) as judged from the eventual appreciation of more definitive information (e.g., autopsy studies)” [27] represented a milestone in studies and research for better understanding the frequency and nature of these problems as well as related subsequent adverse events or inefficiencies in patient care. The previously described research tracks are actually converging and demonstrate the existence of a substantial number of failures in the interface between clinic and laboratory sides, and the need that laboratories and physicians can “understand their mutual ownership and work together to ensure that patients are more safe” [28].

CCLM and patient safety: the special issue in 2007

The evidence of the nature of laboratory errors and their role in the international agenda for patient safety was clearly understood and emphasized by the World Health Organization (WHO) Envoy for Patient Safety, Sir Liam Donaldson, in the Foreword of the Special issue of Clinical Chemistry and Laboratory Medicine dedicated to “Laboratory Medicine and Patient Safety” [29]. This foreword represents a milestone in the path towards a new deal in the laboratory approach to errors and patient safety. First, it recognizes that “timely and accurate laboratory test results
are a cornerstone of effective diagnosis and treatment of patients”. Second, it gives emphasis to the aspect that “laboratory medicine already has a long history of careful attention to quality assurance, standard setting and performance monitoring” but that the complexity of laboratory testing makes it “not safe as it could or should be”. Third, it underlines that “many of the errors in laboratory medicine occur in the pre- and post-analytical phases, rather than within the walls of the laboratory”, and that they may result in “unnecessary treatments and follow-up of tests and inaccurate diagnosis of patients”. Finally, it recognizes the need of “a better inter-departmental cooperation to improve the quality of specimen collection and data dissemination”. The entire special issue of the Clinical Chemistry and Laboratory Medicine (CCLM) journal is a valuable source of knowledge on the issue of laboratory errors and patient safety, but some papers deserve major consideration. Laposa and DiGe have produced a seminal paper for the need for a deeper understanding of the problems in pre- and post-analytical phases [30]. In fact, the authors focus the readers attention on the initial steps, namely test selection, that have been termed “pre-pre-analytical” and on the final activities, namely test interpretation, that have been called “post-post-analytical”. The take-home message is the need to “train future pathologists regarding the meaning of clinical laboratory test results and interact with clinicians in a consultative partnership”. The paper by Lippi and Guidi mainly focuses on risk management strategies in pre-analytic steps, moving the issue of laboratory errors from the identification of their incidence and nature to the prediction of accidental events, increase and diversification of defences and a decrease in the vulnerability of procedures. The authors stress the point that “patient safety must be fully integrated with other critical requirements and standards for clinical laboratories” and, therefore, “full implementation of risk management and total quality systems should be regarded as a separate activity, but should be integrated within the everyday practice of laboratory professionals” [31]. Another seminal paper in the special issue describes a new method for managing laboratory risks, based on a combination of different risk analysis methodologies, i.e., cognitive task analysis, Human Hazard and Operability Study, Absolute Probability Judgment and Analytical Hierarchical Process. The method, evaluated by five clinical laboratories in Italy, was found to be a reliable tool for risk management, as strategies based on process analysis seem to offer a unique opportunity for detecting laboratory errors that cannot be identified through previously adopted quality control and assessment programs [32]. Since pre-analytical procedures have been found particularly vulnerable to error, the following article on recommendations for detection and management of unsuitable samples represents another milestone in the projects aiming to reduce the error risk, namely because achieving consensus on detection and management of unsuitable specimens is an essential pre-requisite for any further initiative. The recommendations are based on the widely accepted grading system on a scale from A to E, for supporting their strength [33]. It is well-known that most unsuitable samples are due to misidentification, quantity (insufficient volume, inadequate blood/anticoagulant ratio) or quality issues (hemolytic, clotted, contaminated specimens, or samples collected in the wrong container), but corrective and predictive actions are not so obvious. This special issue also provides interesting papers on the point-of-care testing (POCT) and related potential errors [34], and in particular the issue of patient safety in arterial blood gas analysis [35]. Almost all the insights described in this issue of the journal have been taken into consideration in another paper which represents a useful description of the state-of-the-art but, in addition, paves the way to further studies and initiatives, that have been collectively termed “the agenda for tomorrow” [36].

CCLM and patient safety: after the special issue

Starting from 2007, and after the release of the special issue, the journal has published an increasing number of papers dealing with laboratory errors and patient safety, representing a friendly house for authors who have been, and will be interested to work in these fields. I would like to recognize only some of the papers that seem to be particularly representative of the advancements in this area. In 2008 a collective paper on hemolysis, which represents the leading cause of unsuitable specimens, described the most prevalent causes of this phenomenon, as well as actions to correctly manage, correct and prevent it, thus avoiding risk for patient care [37]. One year later, some of the authors of the previously described paper, took a further step in the management of hemolytic specimens describing the results of a multicenter evaluation of the hemolysis index, an automated and objective mean for identifying hemolysis in clinical practice and, therefore, for an “evidence-based” management of patient samples [38]. The improvements in pre-analytical quality are the subject of another milestone in the field, a collective paper which summarized the work done in the pre-analytic area and suggested further steps in projects aiming to reduce
errors in the initial steps of the loop [39]. This article provided a significant update on the total quality management of the pre-analytical phase, encouraging further improvements through the identification of bottlenecks in the process, underlining the need for a better training and audit for operators involved in specimen collection/handling procedures, and emphasizing the importance of process monitoring through valuable and reliable quality indicators. As patient/samples misidentification represents a major issue and the first goal in quality improvements in laboratory medicine, the article by Dhatt and Col leagues was particularly welcomed, as it provided further evidence of this type of errors in the era of wristband and information technology facilities [40]. Other sources of variability in the pre-analytical phase are represented by specimen handling and transportation, and some articles underlined the need of improving current evidence on the effects of pneumatic tube transport on chemistry, hematology and coagulation tests [41, 42].

As the analytical quality still represents a non-negligible cause of diagnostic errors and risk of errors, along with papers that report on new tests, reagents and instrumentations (e.g., highlighting that carryover still affects the analytical quality of some chemistry analyzers) [43], the journal has stimulated the debate on quality specifications [44], permissible limits for analytical imprecision and bias [45, 46], the concept of uncertainty of measurement [47], as well as the application of traceability concepts to analytical quality control [48].

Improvements in the post-analytical phases have been reported by describing automated systems for verification, validation and delivery of laboratory results [49], as well as new intriguing proposals for a better presentation of laboratory results [50–53]. In addition, the quality of interpretative comments [54] and policies for critical values reporting [55, 56] were topics for other interesting papers, and for a paper which specifically addresses the challenges in reporting hemostasis assays to assure a safer interpretation of results [57]. A special issue dedicated to reference values has been recently published to update this issue that still plays a fundamental role in assuring an appropriate and safe interpretation of laboratory results [58]. It is noteworthy that the journal has a long history and tradition in studies and publications regarding reference values, a topic in which it would like to maintain a leadership by supporting the efforts of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the European Federation of Clinical Chemistry (EFCC) and other professionals committees.

In addition, a series of papers has also been published on quality indicators in extra-analytical phases, whereby it underlined the importance of these tools for identifying and improving procedures and processes that may be vulnerable to errors in the initial and final steps of the loop. Two groups from Spain have published papers on proposed quality indicators (QIs) in extra-analytical phases of the testing process [59, 60] paving the way to further advancements in this area. As a result of the increasing interest for the development and monitoring of QIs, the IFCC has launched a working group on “laboratory errors and patient safety” which has published in the journal a report on the preliminary evaluation of 25 quality indicators (16 in the pre-analytic, four in the analytic and five in the post-analytic phase) covering all phases of the total testing process, thus promoting the information and the request for enrolling an increasing number of clinical laboratories that may take part in the project [61]. Even more recently the journal has published the experience of a clinical laboratory that has collected data on 38 QIs over a 3-year time interval, demonstrating that processes and indicators under the direct control of the clinical laboratory had improved much more than those requiring co-operation between the laboratory and care teams [62]. While this result should be easily predicted on the basis of the complexity of processes at the boundaries between laboratory and the clinic, it further supports the evidence that a major cooperation and partnership is advisable at the clinical-laboratory interface to really improve patient safety. The journal has promoted and stimulated the publication of papers dealing with errors and patient safety not only in clinical laboratories but also, for example, in transfusion medicine [63]. Finally, the journal has recently promoted an important debate about the problem of antidoping testing, health safeguard in sports and fair competition, highlighting quality issues, essential pre-analytical and analytical requirements as well as potential drawbacks in conventional antidoping tests, especially for the hematological parameters currently included within the Athlete Biological Passport [64–68].

Conclusions

The best way to celebrate the “first” 50 years of our journal is to assure it a long and important future by designing a pathway aiming to provide real value for readers and authors. Quality represents a fundamental requisite in the delivery of laboratory services. In particular, in laboratory medicine quality is a rather broad term that covers the entire spectrum of the total testing process and that, ultimately, should assure safer care, better use of economical and human resources and – last but not least – effective clinical outcomes. We do know
that testing errors affect patient care. Errors in analysis have been reported to be related to adverse clinical interventional activities [69]. However, inappropriate testing, both over- and under-utilization, and other failures in pre-pre-analytical activities can be frankly misleading as they may lead to adverse events, further unnecessary investigations and clinical interventions. Defects in post-analytical steps may also affect patient safety, and vice versa, a timely communication of critical values can be lifesaving [70]. Therefore, a comprehensive approach to quality and safety in laboratory medicine has still to be built upon the concept of the brain-to-brain loop [71]. As quality is a never ending journey, Clinical Chemistry and Laboratory Medicine would like to remain an important partner in this journey, assuring evidences, updates and new insights, thus stimulating laboratory professionals to improve the delivery of laboratory services to ultimately assure a safer care.

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