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Research Article

Pre-Analytical Laboratory Errors and Their Impact on Diagnostic Accuracy

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Abstract:

Pre-analytical laboratory errors refer to the mistakes that occur before the actual analysis of biological specimens, significantly impacting the overall accuracy of diagnostic testing. These errors can arise from various sources, including patient misidentification, improper collection techniques, inadequate specimen handling, and delays in transportation. For instance, if blood samples are not drawn using the correct technique, it may result in hemolysis, contamination, or inaccurate volumes, which could lead to false positives or negatives. Furthermore, the lack of standardization in sample collection and processing procedures across different facilities can exacerbate these issues, emphasizing the critical need for stringent protocols and training. The implications of pre-analytical errors on diagnostic accuracy can be profound, affecting patient outcomes and healthcare decision-making. An inaccurate test result may lead to misdiagnosis, inappropriate treatment plans, and ultimately adverse patient consequences. For healthcare providers, understanding and addressing these errors is essential for enhancing the reliability of laboratory results. Implementing quality control measures, staff training, and adopting automation in specimen handling can mitigate risks associated with pre-analytical errors, thereby improving overall laboratory quality and patient safety. Investing in these areas is crucial, as accurate and reliable diagnostics are fundamental for effective clinical management and optimal patient care.

1. Introduction

The modern healthcare delivery system is fundamentally reliant on the data generated by clinical laboratories. It is estimated that approximately 70% of all medical decisions, including diagnosis, treatment, monitoring, and prognosis, are based on information derived from laboratory test results [1]. This profound dependence places an immense responsibility on the laboratory to provide accurate, reliable, and timely data. The concept of diagnostic accuracy, therefore, is not merely an abstract scientific ideal but a critical pillar of patient safety and effective clinical management. Inaccurate results can lead to misdiagnosis, inappropriate or delayed treatment, unnecessary further testing, and ultimately, patient harm, while also incurring significant additional costs for healthcare systems [2].To ensure the integrity of laboratory data, the total testing process is conceptually divided into three distinct phases: pre-analytical, analytical, and post-analytical. The analytical phase, which encompasses the actual performance of the test on the specimen within the controlled environment of the laboratory, has historically received the most attention and investment. Through advancements in automation, standardization, and internal quality control procedures, laboratories have achieved a remarkable degree of precision and accuracy during this phase [3]. Similarly, the post-analytical phase, involving result validation, interpretation, and reporting, has benefited from sophisticated laboratory information systems (LIS) and electronic health records (EHR), which have streamlined communication and reduced transcriptional errors.

In stark contrast, the pre-analytical phase remains the most vulnerable and error-prone segment of the total testing process. This phase encompasses all procedures from the clinician's test selection and request, through patient preparation and identification, specimen collection, handling, transportation, to the final acceptance and processing of the specimen in the laboratory prior to analysis. It is a complex, multi-step workflow that often occurs outside the direct and controlled environment of the laboratory, involving a diverse array of personnel including physicians, nurses, phlebotomists, and transport staff, many of whom may not be under the laboratory's direct supervision [4].Extensive literature over the past two decades consistently identifies the pre-analytical phase as the primary source of errors in laboratory medicine. Studies indicate that pre-analytical errors account for 46% to 68% of all laboratory mistakes, significantly outnumbering those occurring in the analytical (7%–13%) and post-analytical (18%–47%) phases [5, 6]. This disproportionate distribution highlights a critical gap in quality management. The consequences of these errors are far-reaching. A compromised specimen can lead to an analytically precise result that is clinically misleading, rendering even the most sophisticated laboratory instrumentation unreliable. For instance, a hemolyzed sample can cause falsely elevated potassium, lactate dehydrogenase (LDH), or aspartate aminotransferase (AST) levels, potentially mimicking life-threatening conditions like hyperkalemia or myocardial infarction [7].The impact extends beyond individual patient misdiagnosis. Pre-analytical errors contribute to diagnostic delays, require specimen recollection causing patient discomfort and anxiety, increase laboratory workload through unnecessary repeat testing, and waste valuable resources. In an era

emphasizing evidence-based medicine and cost containment, the economic burden of these errors is substantial, costing healthcare systems millions annually in wasted reagents, labor, and clinical mismanagement [8].

2. Patient Identification and Request Errors: The Foundational Failure

The pre-analytical process begins not at the moment of venipuncture, but with the clinician's test request and the unambiguous identification of the patient. Errors at this initial, foundational stage can irrevocably compromise the entire testing process, regardless of how perfectly the subsequent steps are performed. Patient misidentification is arguably the most serious pre-analytical error, as it represents a total failure of the chain of custody for the specimen. This can occur through mislabeling of collection tubes, applying labels intended for another patient, or drawing blood from the wrong patient altogether [9]. The consequence is a analytically valid result placed in the wrong patient's record, which can lead to catastrophic clinical actions, such as withholding necessary treatment from one patient while administering potentially harmful therapy to another based on foreign laboratory data [10].Closely related are errors in the test request itself. Inappropriate test selection, whether due to a lack of clinical information, outdated order sets, or simple human error, leads to unnecessary testing and wasteful expenditure. More insidiously, the omission of a crucial test can delay diagnosis. The adequacy of clinical information provided on the request form is another critical factor. The absence of relevant data—such as the patient's age, sex, clinical diagnosis, time of collection, or current medication—can hamper the pathologist or clinical scientist's ability to interpret results accurately, especially for tests with broad reference intervals or known drug interferences [11]. In the era of electronic ordering, while reducing illegibility, new errors can emerge, such as duplicate orders or "clone" errors where an order set from one patient is inadvertently applied to another [12]. These errors underscore that the pre-pre-analytical steps, occurring before the specimen is even collected, set the stage for all that follows and require rigorous protocols involving at least two patient identifiers (e.g., full name and date of birth) and active verification processes.

3. Specimen Collection Errors: The Source of Major Pre-Analytical Variability

The act of specimen collection is a critical intervention that, if performed incorrectly, can alter the composition of the sample and introduce artefacts that directly affect analyte stability and measurement. Among the most common collection-related errors is hemolysis, the rupture of red blood cells and release of their intracellular components into the serum or plasma. Hemolysis can be caused by improper venipuncture technique (e.g., using a needle that is too small, excessive suction with a syringe, probing for a vein), forced transfer of blood through a needle, or vigorous mixing of tubes [13]. The impact on diagnostics is profound: potassium, LDH, AST, and phosphorus are markedly elevated, while other analytes can be decreased due to dilution or interference. For example, hemolysis can falsely lower insulin measurements due to proteolytic degradation by enzymes released from cells [14]. Clinically, pseudohyperkalemia due to hemolysis can trigger unnecessary and potentially dangerous interventions for non-existent hyperkalemia.The volume of blood collected is another crucial parameter. Underfilled coagulation tubes (e.g., citrate tubes for PT/INR and aPTT) create an excess of anticoagulant relative to plasma, leading to an artificially prolonged clotting time and falsely elevated INR results, which could incorrectly suggest a need to reduce warfarin dosage [15]. Overfilling blood culture bottles can dilute the broth and potentially reduce the sensitivity for detecting microorganisms. The use of incorrect collection tubes represents a direct failure of protocol. Drawing blood for trace metal analysis into a conventional tube with a rubber stopper can contaminate the sample with zinc. Using a serum separator tube for certain therapeutic drug monitoring tests (e.g., tacrolimus) can lead to inaccurate results due to drug adsorption by the separator gel [16].Tourniquet application time is a frequently overlooked variable. Prolonged venous stasis (more than one minute) can cause hemoconcentration, increasing the concentration of protein-bound and large molecules by up to 10-15%. This leads to falsely elevated values for total protein, cholesterol, calcium, and coagulation factors [17]. Patient posture during collection (supine vs. upright) similarly affects plasma volume and can alter concentrations of hormones like aldosterone and renin. Even the order of draw, if not followed meticulously, can introduce contaminants; for instance, drawing a citrate tube after an EDTA tube can carry over EDTA, which chelates calcium and invalidates coagulation studies [18].

4. Patient Preparation and Physiological Variables: The Uncontrolled Confounders

Laboratory results are not only a reflection of disease but are also influenced by a multitude of patient-specific factors that, if not considered, become sources of pre-analytical error. Failure to adhere to or document patient preparation protocols is a major contributor. The most common instruction is fasting. Non-fasting samples show elevated levels of triglycerides, glucose, and insulin, while other analytes like phosphate and bilirubin may decrease postprandially [19]. For tests like glucose tolerance tests or lipid profiles, strict fasting is mandatory for accurate interpretation. Similarly, the timing of specimen collection is critical for tests with diurnal variation, such as cortisol (peak in early morning), TSH (higher at night), and iron (higher in morning) [20]. A cortisol level drawn in the afternoon may fall within the reference interval, masking a morning deficiency indicative of adrenal insufficiency.

Physical activity is a potent physiological modulator. Strenuous exercise can cause transient increases in creatine kinase (CK), lactate, uric acid, and white blood cell count, while decreasing serum iron [21]. Even routine ambulation before a blood draw can alter plasma volume. Emotional stress can trigger the release of adrenaline and cortisol, leading to increased glucose, free fatty acids, and white blood cells. The menstrual cycle profoundly affects hormone levels (estrogen, progesterone, LH, FSH) and also influences parameters like iron stores, which decrease during menstruation [22].

Perhaps the most complex confounding factor is medication. Drugs can interfere with laboratory assays through pharmacological (in vivo) or analytical (in vitro) mechanisms. Pharmacologically, diuretics affect electrolytes, oral contraceptives alter clotting factors and lipids, and corticosteroids influence glucose and white cell counts. Analytically, high doses of vitamin C can cause false-negative results for fecal occult blood using guaiac-based tests, while acetaminophen can interfere with some dry chemistry methods for creatinine [23]. Herbal supplements are an increasing concern; for example, St. John's Wort induces liver enzymes, lowering the concentration of drugs like cyclosporine, which is monitored therapeutically. A comprehensive medication history is, therefore, an indispensable part of the pre-analytical information set.

5. Specimen Handling and Transportation Errors: The Degradation Pathway

Once collected, the integrity of the specimen must be preserved throughout its journey to the laboratory. Errors in handling and transportation can induce chemical and cellular changes that degrade sample quality. Temperature control is paramount. Many analytes are thermolabile. For instance, ammonia levels increase rapidly at room temperature due to deamination of amino acids by blood cells, requiring immediate icing and prompt analysis [24]. Conversely, cooling whole blood can increase potassium levels as it is released from cells. Enzymes like acid phosphatase are particularly unstable. Delayed separation of serum or plasma from cells is a major cause of error. Prolonged contact leads to glycolysis by red and white cells, causing a clinically significant decrease in glucose (approximately 5-7% per hour at room temperature) and a parallel increase in lactate [25]. Potassium leaks from cells into serum, and inorganic phosphate increases due to hydrolysis of organic phosphates.

Exposure to light is critical for photosensitive analytes. Bilirubin, especially the unconjugated fraction, can degrade by up to 50% when exposed to direct sunlight or fluorescent light for an hour, leading to a false underestimation of neonatal jaundice severity [26]. Vitamin B2 (riboflavin) and B6 are also light-sensitive. Proper mechanical handling is essential to prevent hemolysis and cell lysis. Excessive agitation during transport, improper tube orientation, or exposure to vibration can damage cellular components. For microbiology specimens, delays in transport can allow overgrowth of contaminants or the death of fastidious pathogens, reducing culture sensitivity [27].The efficiency of the transport system itself is a systemic factor. Long transit times, especially without proper temperature stabilization, degrade sample quality. Inadequate packaging for samples transported by courier can lead to breakage, leakage, or temperature excursions. The use of pneumatic tube systems, while efficient, can cause hemolysis in certain sample types if the acceleration, deceleration, or impact forces are excessive, particularly for delicate samples like those for blood gas analysis or coagulation studies [28]. Establishing and monitoring defined turnaround times for transport and implementing standardized, validated transport containers are essential quality measures.

6. Specimen Processing and Laboratory Acceptance Errors

Upon arrival in the laboratory, the specimen undergoes a reception and triage process. Errors at this stage can allow unsuitable samples to enter the

analytical workflow. The initial visual inspection is crucial but subjective. Laboratory personnel must check for labeling discrepancies, tube type appropriateness, volume adequacy, and signs of visible hemolysis, icterus, or lipemia (HIL indices). Lipemia, caused by high concentrations of chylomicrons following a fatty meal or in certain dyslipidemias, causes turbidity that scatters light and leads to falsely elevated readings for hemoglobin, bilirubin, and many other analytes measured by photometry [29]. While modern analyzers can detect and flag HIL, visual inspection remains the first line of defense.Centrifugation conditions are a standard but critical processing step. Inadequate centrifugation speed or time leads to incomplete separation of serum/plasma from cells, resulting in residual platelets (platelet-poor plasma is required for many coagulation tests) or cellular contamination that can interfere with assays and cause carryover in automated pipettors [30]. Centrifuging specimens before complete clotting (for serum tubes) can cause fibrin strand formation, which may clog analyzer probes. Altering the specified centrifuge time or speed protocol constitutes a processing error.The stability of analytes in separated serum or plasma is not infinite. Even when stored at recommended temperatures (e.g., 4°C), some analytes degrade over time. For example, parathyroid hormone (PTH) is unstable and should be frozen if analysis is delayed. Aliquoting errors, where a sample is divided into smaller portions for different tests, can lead to cross-contamination if proper pipetting technique is not used or if the same pipette tip is reused [31]. Finally, the laboratory's sample acceptance and rejection policy is the final gatekeeper. A clear, standardized policy that defines rejection criteria (e.g., mislabeled, unlabeled, grossly hemolyzed, insufficient volume for the test ordered) and a consistent process for communicating with the clinical team to request recollection are essential to prevent the analysis of compromised specimens. Failure to reject a faulty specimen is, in itself, a significant pre-analytical error.

7. Impact on Specific Diagnostic Areas

The effects of pre-analytical errors are not uniform across all laboratory disciplines; they have distinct and sometimes severe consequences in specialized areas. In hematology and coagulation, proper specimen integrity is paramount. Clotted samples, often due to inadequate mixing or delayed mixing of EDTA tubes, will trigger a clot flag on automated analyzers and invalidate complete blood count (CBC) parameters, especially platelet counts, which may be falsely low [32]. Microclots can go undetected and cause erroneous results. For coagulation studies, the blood-to-anticoagulant ratio in citrate tubes must be exact; underfilling by as little as 10% can significantly prolong PT and aPTT. Traumatic venipuncture, activating the coagulation cascade, can also shorten clotting times, masking a true coagulopathy.Clinical chemistry is perhaps the most affected by pre-analytical variables, as detailed earlier. Enzymes like CK and LDH are sensitive to temperature and delay. Electrolytes are affected by hemolysis (K^+), evaporation (increased Na^+), and contamination (e.g., K^+ from EDTA tube carryover). Hormone assays, often employing sensitive immunoassays, can be impacted by heterophilic antibodies from the patient, which are an in vivo interferent, but sample handling can affect the stability of labile hormones like ACTH and gastrin [33].In microbiology and serology, the pre-analytical phase is arguably the most important determinant of test utility. The quality of the specimen directly dictates the likelihood of detecting a pathogen. Sputum samples contaminated with oral flora, improperly stored stool samples for parasite examination, or swabs that have dried out will yield negative results despite active infection. Blood cultures drawn without proper skin asepsis lead to contamination with skin commensals like *Staphylococcus epidermidis*, causing false-positive results that trigger unnecessary antibiotic therapy and extended hospitalization [34]. For viral load testing (e.g., HIV, HCV), improper handling can lead to degradation of viral RNA, causing falsely low or undetectable results.Transfusion medicine presents zero-tolerance scenarios. An error in patient identification during blood sample collection for type and screen or crossmatch can have fatal consequences if it leads to the transfusion of incompatible blood. Mislabeling of the donor unit or the recipient sample are catastrophic pre-analytical failures [35]. In histopathology and cytology, pre-analytical errors include inadequate fixation of tissue biopsies (leading to autolytic changes), incorrect fixative use (e.g., using formalin for electron microscopy specimens requiring glutaraldehyde), or loss of specimen during transfer from collection container [36]. These errors can compromise morphological assessment and ancillary tests like immunohistochemistry.

8. Strategies for Mitigation and Prevention: A Systems Approach

Addressing the multifaceted challenge of pre-analytical errors requires a systematic,

multidisciplinary approach that extends beyond the laboratory walls. Education and continuous training are the cornerstones. All personnel involved in the testing process—clinicians, nurses, phlebotomists, and transport staff—must receive standardized, competency-based training on proper procedures, the rationale behind them, and the potential consequences of errors [37]. This training should be periodic and include updates on new collection devices or protocols.

Technological interventions offer powerful tools for error reduction. Electronic ordering with clinical decision support can reduce test request errors by flagging duplicate orders, suggesting appropriate tests based on diagnosis, and requiring essential clinical information. Barcode technology for patient identification and specimen labeling, when integrated with a positive patient identification (PPID) system at the bedside, virtually eliminates misidentification errors [38]. Automated tube labelers and pre-printed labels also reduce manual labeling mistakes. Automated transport systems and tracked courier services can improve turnaround time and allow for monitoring of transport conditions.

The implementation of a robust Quality Management System (QMS) specific to the pre-analytical phase is essential. This includes the development of clear, detailed, and accessible standard operating procedures (SOPs) for every step. Key performance indicators (KPIs), such as sample rejection rates, hemolysis rates, and mislabeling rates, should be continuously monitored, benchmarked, and reviewed in quality meetings [39]. Root cause analysis (RCA) should be performed for all significant errors to identify systemic flaws rather than attributing blame to individuals.

Finally, fostering effective communication and collaboration between the laboratory and clinical services is vital. The laboratory must be proactive in communicating rejection reasons and providing feedback on common errors. Establishing a laboratory-phlebotomy committee or having laboratory representatives participate in clinical safety rounds can bridge the gap, promote a shared understanding of the process, and facilitate the joint development of solutions to persistent problems [40]. A culture of safety, where errors are reported without fear to facilitate learning and system improvement, is the ultimate goal.

10. Conclusion

The pre-analytical phase represents the most critical and vulnerable frontier in the pursuit of diagnostic accuracy. As this comprehensive analysis demonstrates, errors can infiltrate every step, from test selection and patient identification to collection, handling, and initial processing. These errors are not mere technical oversights; they have direct, measurable, and sometimes dangerous impacts on laboratory results, leading to misdiagnosis, inappropriate treatment, patient harm, and significant economic waste. The diversity of error types—from identification failures and improper technique to unmanaged physiological variables and specimen degradation—underscores the complexity of the challenge.

Overcoming this challenge is imperative. It requires a paradigm shift from viewing the laboratory as an isolated analytical service to understanding it as an integral part of a total testing process, the majority of which occurs outside its physical walls. A relentless focus on systems-based solutions—encompassing continuous education, strategic technological investment, rigorous quality management, and deepened clinical-laboratory collaboration—is the only path forward. By systematically fortifying the pre-analytical phase, healthcare systems can significantly enhance the reliability of laboratory data, thereby fulfilling the fundamental promise of laboratory medicine: to provide an accurate foundation for clinical decision-making and to contribute meaningfully to improved patient outcomes and safety. The goal must be to ensure that the patient's biological truth is faithfully transmitted from the bedside to the laboratory report, undistorted by preventable pre-analytical variables.

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