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# Pre- and postanalytical errors in haematology

Barbara De la Salle

West Herts Hospitals NHS Trust, UK NEQAS Haematology, Watford, UK

**Correspondence**
Barbara De la Salle, West Herts Hospitals NHS Trust, UK NEQAS Haematology, Watford, UK.
Email: barbara.delasalle@nhs.net

## Abstract

The majority of errors in laboratory medicine occur in the pre- and postanalytical phases of the testing process. Although the causes of these errors are largely common to all laboratory medicine specialties, it is important for the haematology laboratory to understand the particular impact of some on automated counting. The preanalytical phase is the stage of greatest risk but preanalytical errors may go undetected until postanalytical validation and interpretation. The challenges in the postanalytical phase include the standardisation of reference intervals against which results can be interpreted and the impact of just a small difference in reference interval for a key analyte such as haemoglobin concentration. Quality indicators against which pre- and postanalytical error incidence are measured are a source of information that can be used to improve services but laboratories struggle to collect good quality data.

**KEYWORDS**

automated cell counting, general haematology, postanalytical, preanalytical, quality indicators

## 1 | INTRODUCTION

Much of the improvement in the quality of laboratory testing in recent decades has focused on what happens to the specimen during the analytical or laboratory testing phase, which lends itself to standardised processing, statistical internal quality control (IQC) and external quality assessment or proficiency testing (EQA/PT). There is a substantial body of evidence that the remaining areas for improvement in laboratory medicine-related error rates are in the preanalytical and, to a lesser extent, the postanalytical phases. Although the overall error rate in laboratory medicine is relatively low compared to other areas of medicine,[1] a key examination of laboratory errors in a stat laboratory in Italy showed that 62% of errors were the result of events in the preanalytical phase, before the specimen reaches the laboratory bench, and a further 23% after testing is complete; figures that were similar to those from 10 years earlier.[2] The impact of these errors may be significant. If the error is detected before the result is issued, for example through delta checking or a change in a genetically-determined factor (such as an ABO blood group), it may cause a delay in diagnosis or treatment, inconvenience and anxiety for the patient and, in some cases, a missed opportunity for diagnosis or screening if the specimen cannot be retaken. Errors that go undetected may result additionally in an incorrect or missed diagnosis, unnecessary investigation or treatment and endanger patient safety. A lack of attention to preanalytical errors and a focus just on quality in the analytical phase has potential for patient harm,[3] and all laboratory medicine errors are a drain on healthcare resources. The gap between the proportions of analytical and extraanalytical error rates has been described as an "Iceberg of Errors",[4] which should be accounted for as part of measurement uncertainty.[5] This article will review some of the sources of error in the pre- and postanalytical phases in haematology, with particular emphasis on their impact in automated cell counting.

## 2 | THE TOTAL TESTING PROCESS IN LABORATORY MEDICINE

Diagnostic testing falls into three broad phases that make up the total testing process (TTP): the preanalytical phase, or what

  

happens to the specimen prior to analysis, the familiar analytical phase and the postanalytical phase, which includes interpretation and reporting of the result obtained. Lundberg described the TTP in terms of a "brain-to-brain" loop of nine steps from the brain of the requesting physician through test ordering, specimen collection, identification (specimen and patient), transportation, preparation, analysis and concluding with the return of the result to the requesting physician.[6] Later, additions to this model added interpretation (by both the laboratory and the requesting physician) and reporting of the result to the patient (action),[7] which have been described as a post-postanalytical phase. Lundberg has also suggested that the process should be extended to require an assessment of the effectiveness of the testing in terms of public good or improvement in public health.[8]

The concept of the pre-preanalytical phase has also been introduced to the TTP, although the differentiation between this and the preanalytical phase is variable. The pre-preanalytical phase has been described as the stage in which the requesting physician formulates the appropriate question upon which the test request is based and selects the tests to be undertaken.[9] Plebani[10] on the other hand describes the pre-preanalytical phase as being all the steps that occur prior to receipt of the specimen by the laboratory (ie test requesting, patient identification, specimen collection and transport) with the preanalytical phase being the processes such as numbering, verification, centrifugation and separation, which occur as part of the preparation of the material for analysis within the laboratory.

The proportion of errors in each phase of the TTP, as described by Plebani,[10] is shown in Table 1.

In a comprehensive review of quality indicators in laboratory medicine, Shahangian and Snyder[11] identified six stages in the TTP with a total of fourteen possible quality indicators, related to the Institute of Medicine (IoM) health care domains. The six stages are (a) test ordering, (b) patient identification and specimen collection, (c) specimen identification, preparation and transport, (d) analysis, (e) reporting and (f) interpretation and action. Although there are similarities in the description of the TTP phases and the quality indicators, the lack of standardisation in both the number of indicators and the terminology used in the TTP has the potential to confound data collection and error monitoring.

Other potential sources of extraanalytical error in laboratory medicine have been suggested, for example lack of financial and staff resources, lack of standardisation and poor organisation of services[7] although these aspects may be better monitored as part of the accreditation of the management competence of an organisation to provide a clinical diagnostic service. The ISO 15189: 2012 Medical laboratories—Requirements for quality and competence standard requires laboratories to take a responsibility for the TTP and to demonstrate a process for monitoring errors and nonconformances outside the analytical phase.

The incidence of diagnostic errors is difficult to assess and may be underestimated[12]; it has been suggested that 12 million adults annually in the United States of America suffer a diagnostic error, half of which are significant.[13] Errors that directly affect the diagnosis, treatment or advice given to a patient, for example an incorrect ABO blood group, an incorrect genetic test outcome, an incorrectly identified infectious agent or an incorrect cellular pathology assessment have a clear and possibly catastrophic impact on patient safety. Much more difficult to detect are those that result in a clinically unnoticed quantitative error, for example a patient or specimen identification error that leads to the transposition of one normal complete blood count (CBC) result for another, which may not cause patient harm but will lead to the underestimation of the actual error rate and the loss of the opportunity for root cause analysis.

## 3 | THE PREANALYTICAL PHASE: FROM THE PATIENT TO THE LABORATORY BENCH

Errors in test selection and ordering, patient identification and specimen labelling are pan-disciplinary and will not be discussed in this manuscript with particular reference to haematology. The magnitude of these errors in terms of best use of healthcare resources and potential for patient harm is applicable in all laboratory medicine specialties. The authors would support, however, an approach to specimen identification and labelling similar to that used to resolve "wrong blood in tube" incidents in blood transfusion.[14]

**TABLE 1** Estimated proportions of errors in the phases of the total testing process (TTP), as defined by Plebani[10]

| TTP phase | Examples of error | Estimated proportion of errors |
|---|---|---|
| Pre-preanalytical | Test ordering, patient identification, patient preparation, sample collection, sample quality, transportation, storage | 46%-68% |
| Preanalytical | Sample sorting, centrifugation, labelling, separation | 3%-5% |
| Analytical | Sample analysis | 7%-13% |
| Postanalytical | Validation, interpretation, turnaround time, critical value reporting | 13%-20% |
| Post-postanalytical | Interpretation, delayed reaction, lack of follow-up or referral | 25%-46% |

### 3.1 | Patient preparation

Physical activity has been identified as an important preanalytical variable,[15] and the European Federation of Laboratory Medicine (EFLM) advises that patients abstain from excessive or unaccustomed exercise for 24 hours prior to routine phlebotomy.[16] An increase in the white blood count (WBC), neutrophil count, platelet count, red cell fragmentation and platelet activation has been reported post-marathon running.[17] Sustained exercise produces an increase in plasma volume (PV),[18] which may lead to a decrease in haemoglobin (Hb), red blood cells (RBC) and haematocrit (Hct) in athletes in training programmes. The status of the patient, therefore, needs to be understood in the interpretation of results against standard reference intervals. Since the physiological response to exercise will be affected by the physical fitness of the individual, it is important to distinguish between the effects of sustained training from episodes of unaccustomed, intense exercise in an otherwise sedentary individual.[19,20]

Patient posture has for some time been implicated in variation in the CBC.[21] The EFLM recommendation is that patients should rest for fifteen minutes in a seated position prior to phlebotomy as a standardised approach to phlebotomy procedures.[16] The impact of posture is as a result of changes in PV from the supine to the upright position and the consequence of this on Hb, cell counts and Hct. The potential clinical impact of postural changes in the CBC when assessing a patient is illustrated by a spurious case of anaemia in a patient without blood loss or intravenous infusion that resulted from changes in posture between consecutive blood samples. In this case, the author described a 10%-15% reduction in Hb, Hct, WBC and platelet count after the patient had been lying down for two hours, in comparison to an earlier specimen, taken without rest, immediately after she had presented at the Emergency Department.[22]

### 3.2 | Specimen collection and specimen quality

Clotted specimens are the most common reason for rejection for automated counting and coagulation. In a large study in China of a total of approximately 10 million haematology samples collected, 57% of the 11 000 rejections were due to specimen clotting,[23] and similar proportions (43%-51%) of specimen rejections because of clotting have been reported in a number of other studies. This high rate of clotted samples is mainly the result of poor phlebotomy and inadequate specimen mixing postcollection. Training of phlebotomy staff and standardisation of phlebotomy practice has been shown to improve specimen quality.[24]

Contamination with infusion fluids when specimens are taken close to an infusion site may be a cause of spurious anaemia and abnormal coagulation test results. Erroneous Hb results from samples taken from a “drip” arm have been implemented in the deaths of patients following unnecessary blood transfusion.[25] Venous stasis of just one to three minutes during venepuncture has also been shown to have an adverse effect on CBC results, leading to an increase in Hb, Hct and RBC.[26] The use of vein-mapping or visualisation technology with the use of infra-red light overcomes the need for a tourniquet to locate a vein.[16]

The anticoagulant of choice for CBC analysis is the di- or tripotassium salt of ethylenediaminetetraacetic acid (EDTA), with a preference for $K_2$EDTA although alternatives (eg magnesium sulphate, $MgSO_4$) may be better for some platelet parameters.[27] The order of draw of specimen types may not affect automated counting results; however, there is a risk of contamination of chemistry and clotting specimens with EDTA and potassium if the CBC specimen is taken first. EDTA tubes have a fixed fill volume that gives the optimum concentration of anticoagulant and both under or overfilling can be a cause of erroneous CBC results. Overfilling the sample risks inadequate mixing prior to testing and may be a cause of a pseudopolycythaemia, pseudothrombocytopenia and pseudoleucopenia, even though the sample is not clotted.[28] Underfilled tubes will result in an increased concentration of EDTA, which may cause platelet volume changes[29] and an excess of $K_3$EDTA has been suggested as a cause of spurious reduction in WBC.[30] More recent work has suggested that underfilled $K_2$EDTA tubes are acceptable for automated counting with just 1.0 mL of blood in a 4 mL tube; however, this work only looked at blood from healthy individuals and one type of analyser.[31] The brand of $K_2$EDTA tube has been shown to be clinically relevant source of variation in mean cell volume (MCV), Hct and platelet distribution width (PDW).[32] Underfilled specimens may also indicate a difficult venepuncture, which in itself may cause platelet activation, platelet swelling and problems with coagulation testing.

There is little evidence that a raised bilirubin causes interference in the CBC unless at very high concentration (greater than 250 mg/L); however lipaemia, for example in a patient on parenteral nutrition, with lipid disorders or post a heavy meal, may affect the platelet and WBC counts as a result of the presence of lipid droplets and may cause sufficient turbidity in the sample to interfere with the Hb[20] (and some other tests, eg the sickle solubility test). The degree of impact may depend upon the type of haematology analyser and the laboratory scientist must be familiar with these confounding factors with their laboratory's technology.

Artificially induced, moderate-to-high haemolysis has been shown to produce a decrease in RBC and Hct and an increase in mean cell haemoglobin (MCH) and platelet count, related to the degree of haemolysis.[33] A major cause of potential haemolysis during specimen collection arises from sample collection through intravenous (IV) catheters. Haemolysis in serum samples taken through IV catheters has been estimated at 29% compared to 1% when a sample is taken by straight needle venepuncture.[34] Similar effects may be seen in patients with severe burns or other conditions with a significant increase in red cell fragmentation or microspherocytes.

### 3.3 | Specimen transport and preparation

All CBC specimens ideally should be analysed within 6 hours of collection, especially where blood cell morphology is required.[35]

Prolonged storage of CBC specimens is a well-recognised cause of an elevated MCV and will also result in morphological changes in the WBC and RBC. Excessive heat or freezing will also render CBC specimens unsuitable for testing. In general, however, time-critical results are defined in haematology in the context of the patient's clinical background, for example WBC and platelet counts in oncology patients, Hb following major blood loss.

There has been debate on the possible impact of pneumatic tube systems (PTS) for specimen delivery on sample quality in blood sciences. PTS delivery has been shown to have minimal or no effect on haematology, coagulation and chemistry results with the exception of patients known to be cytopenic, for example on chemotherapy, where a reduction in an already low platelet count has been reported.[36]

If analysis is delayed, samples are better stored at 2-8°C but this is not advised where the patient is known to have cold agglutinins, which will cause clumping of the red cells and a consequent false elevation of the MCV, reduced RBC and increased mean cell haemoglobin concentration (MCHC).[37] Although haematology analysers with prewarmed reagents may reduce the impact of cold agglutinins, it is not advised to warm the specimens after collection but to re-bleed the patient and keep the specimen warm from the time it taken until it is analysed to ensure an accurate result.[20]

Other than sample reception and verification, there are few preparation steps for CBC specimens, with the exception of adequate mixing prior to analysis. As discussed earlier, this may be hindered by an overfilled specimen.

Table 2 summarises the major confounding factors in the preanalytical phase in terms of the complete blood count.

## 4 | THE POSTANALYTICAL PHASE: FROM THE LABORATORY BENCH TO THE REQUESTING PHYSICIAN

For the purpose of this manuscript, the challenges of test validation and interpretation in the laboratory will be considered rather than report turnaround times and appropriate follow-up by the requesting physician.

### 4.1 | Test validation

Modern automated haematology analysers are complex items of diagnostic equipment able to flag the presence of a potentially spurious result for review and investigation, for example by repeat testing, reflex testing or verification of findings by the microscopic examination of a blood film. The use of delta checks as part of result validation is an important "safety net" that may detect errors in specimen identification and collection, for example specimens diluted with infusion fluid, inadequate mixing due to sample overfilling or with an undetected clot. MCV has been suggested as having the highest positive predictive value of a number of parameters for the identification of specimen mislabelling.[38] Although spurious haematology results usually arise from factors in the preanalytical phase, they may only be detected at test validation in the postanalytical phase through a review of flags, histograms and scatterplots prior to release of the result. Where more basic analysers that do not supply these outputs are used, the user must be aware of the limitations of the methodology and have appropriate backup procedures for review and referral available.

The platelet count may be affected by factors in specimen collection (eg clotting, platelet activation) or related to the individual patient and their clinical condition. Once the latter are identified, then the laboratory can be aware of the phenomenon for future tests. In particular, the presence of EDTA-dependent pseudothrombocytopenia, platelet satellitism, platelet clumping and the presence of giant platelets have been cited as a cause of spurious thrombocytopenia and may also interfere with the provision of an accurate WBC.[19,39,40] As well as RBC fragments and microspherocytes, the presence of cytoplasmic fragments in acute leukaemia, microorganisms in sepsis, cryoglobulins and cryoprecipitates are potential causes of a falsely elevated platelet count, although the extent to which these factors may confound the result will depend on the counting technology used.

Similar factors may interfere with counts of the other cellular blood components: polymorphonuclear cell clumping, which occurs in a small proportion of specimens taken into EDTA, will reduce the total WBC and the neutrophil count.[20,41] A falsely elevated WBC may occur if platelet aggregates, large platelets, nucleated RBC, lysis-resistant RBC and (as before) cryoglobulinaemia or cryoprecipitates are present, as these may be counted as WBC. The Hb and RBC will be affected additionally by a very high WBC (eg greater than $100 \times 10^9$/L) and the RBC to a lesser extent by the presence of giant platelets.

Because a number of reported red cell parameters are derived by calculation, a spurious result in one of the directly measured analytes (Hb, RBC, Hct and/or MCV, depending on manufacturer) may affect the value of any calculated analyte.

### 4.2 | Reference intervals for test interpretation

The postanalytical interpretation of laboratory results relies on the establishment of what is "normal" or expected, the definition of which may be a statistically derived reference interval, a fixed cut-off or an action point. The World Health Organization (WHO) recommends reference intervals for Hb concentration with a lower limit of 130 g/L for the diagnosis of anaemia in adult males, whereas the Centre for Disease Control (CDC) defines the lower limit of Hb concentration as 135 g/L. Although not great, a difference of 5 g/L in the limit for the definition of anaemia may have a significant impact on the numbers of patients diagnosed as anaemic and the consequent rate of referrals to haematology clinics or the number of patients who may benefit from treatment but are missed. Using WHO cut-offs for Hb concentration in women and children, 32.8% of women worldwide are classified as anaemic and 41.7% of children. Kassebaum has estimated the proportion of the world's population

**TABLE 2** Examples of potential sources of preanalytical errors in the automated complete blood count

| Phase of testing | Examples of sources of error | Potential for patient harm |
|---|---|---|
| Preanalytical patient-specific conditions | Cryoglobulinaemia | Spurious cell counts, which may only be detected at result validation or as a result of additional testing |
| | Cold agglutinins | |
| | Lipaemia | |
| | Extreme raised WBC | |
| | WBC fragments | |
| | Giant platelets | |
| | Microspherocytes | |
| | RBC fragments | |
| | Polymorphonuclear clumping | |
| | EDTA-dependent platelet satellitism | |
| Patient preparation | Unaccustomed or extreme physical exercise | Increased WBC, neutrophil count, platelet count |
| | | Reduced RBC, Hb, Hct |
| | | Platelet activation |
| | | RBC fragmentation |
| | Patient posture | Spurious Hb, RBC, Hct |
| | Lipaemia (unfasted patient/postheavy meal) | Spurious Hb, WBC, platelet count |
| Patient identification | Wrong blood in tube | Misdiagnosis |
| | | Delayed testing |
| Sample identification | Inadequate labelling | Rejection of sample leading to delayed testing |
| Sample collection and quality | Incorrect anticoagulant | Rejection of sample leading to delayed testing |
| | Excessive venous stasis<br>Contamination with infusion fluid<br>IV catheter collection<br>Inadequate mixing postcollection<br>Under/overfilled sample | Spurious cell counts as a result of haemodilution/haemoconcentration, haemolysis, excessive EDTA concentration, inadequate mixing during analysis or clots in the sample |
| Sample transportation | Prolonged time in transit<br>Extremes of temperature in transit | Delayed reporting of time-critical results<br>Sample deterioration, especially for cell morphology<br>Increased MCV, MPV<br>Haemolysed sample |
| Sample preparation | Inadequate or excessive mixing prior to analysis | Spurious cell counts |

that is anaemic at 32.9%,[42] highlighting the impact that just a small adjustment in the lower reference interval limit for Hb might have in terms of the incidence of anaemia and the documented global burden of disease.

A recent survey of practice showed a heterogeneous range of lower limits of Hb concentration in practice in haematology laboratories and in how they had been derived, indicating a need for harmonisation.[43] Harmonisation of reference intervals for core tests such as Hb could standardise postanalytical interpretation, make results more "portable" in an era of patient mobility, avoid confusion amongst requesting clinicians and fit better with an increased use of near-patient testing. Establishment of reference intervals by conventional means entails direct testing of specimens from a number of "healthy" individuals; in many cases, these may be preselected from a limited age range, socio-economic status and ethnicity. More recently, indirect methods for setting reference intervals using an evaluation of patients' data have been suggested as a better approach towards harmonisation of ranges.[44] The use of harmonised reference intervals for key analytes such as Hb will not preclude the laboratory from producing local ranges for the purpose of validation but will be a driver for improved traceability of patients' results to higher order reference materials and methods and potentially reduce the variability in the postanalytical phase.

### 4.3 | Critical results reporting

A critical result is one so abnormal as to pose a threat to life unless corrective action is taken promptly. The failure to identify and report a critical result is a major postanalytical error. Review of the literature shows a general consensus in the alert thresholds for haematology results that pose a critical risk.[45] It is essential that each laboratory agrees a critical results action list with requesting physicians and establishes clear lines of communication and responsibility for critical results reporting. Recommendations from the International Council for Standardization in Haematology (ICSH) have summarised consensus critical limits for Hb, WBC and platelet counts, together

with critical blood film findings of acute leukaemia (with more than 20% blast cells), acute promyelocytic leukaemia, thrombotic microangiopathic anaemia, parasites and bacteria.[46]

## 5 | MANAGING WHAT WE STRUGGLE TO MEASURE: MONITORING EXTRAANALYTICAL ERRORS

In order to manage risk in diagnostic testing, the laboratory needs to monitor where errors occur through the use of recognised and standardised quality indicators (QIs). The International Federation of Clinical Chemistry (IFCC) has published a number of standardised QIs for all parts of the TTP.[47] Quality indicators have also been established in Australia, New Zealand, the United States, Brazil, Spain and the United Kingdom, and there are established extraanalytical error-monitoring services offered through EQA/PT providers, for example the College of American Pathologists Q-Probes system, the Key Incident Management and Monitoring System (KIMMS) of the Royal College of Pathologists in Australasia Quality Assurance Program and the UK National External Quality Assessment Scheme's PREPQ pre- and postanalytical quality monitoring service. A common finding from error-monitoring services is that laboratories struggle to collect data despite the general support for error reduction in the extraanalytical phases by the laboratory professions.[48] Collecting good quality data through the use of fewer, standardised indicators incorporated into the laboratory information management system may be the way forward. Monitoring alone is not effective in reducing errors[49] but the information provided can be used at the interface between the laboratory and the clinical user to provide education and/or technological solutions to correct the root cause.[50] Experience from the UK National External Quality Assessment Scheme's PREPQ pre- and postanalytical quality monitoring service, established in 2014, has shown that successful data collection is feasible but requires a culture within the laboratory that values and acts upon the pre- and postanalytical data collected and has at least one committed individual staff member with sufficient technical knowledge and interest to develop systems to extract data from the laboratory information management system (UK NEQAS, unpublished data).

## 6 | CONCLUSION

Healthcare is an activity associated with high risk, and medical error is estimated to be the third leading cause of death in the USA.[51] The laboratory must manage the risk associated with errors in the TTP in order to minimise the contribution of laboratory medicine to this statistic. Many of the errors in the pre- and postanalytical phases in haematology are shared with other specialties but the haematologist must be aware of the confounding factors that are peculiar to the art of automated cell counting. Although the sources of error in the extraanalytical phases are recognised, a consensus on the number and definition of the indicators to monitor is still to be reached. The indicators currently established may require further development to include a patient-centred evaluation of errors and the use of risk-management principles to reduce error rates through education of all staff involved in the TTP. The laboratory must take responsibility for the "end-to-end" management of quality, including corrective action to address the root cause of error in the TTP, to ensure that patients and other users have confidence in the services provided.

## CONFLICT OF INTEREST

The author has no competing interests.

## ORCID


*Barbara De la Salle* https://orcid.org/0000-0002-2926-7441

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