Mini Review

Mads Nybo*, Janne Cadamuro, Michael P. Cornes, Rubén Gómez Rioja and Kjell Grankvist

Sample transportation – an overview

https://doi.org/10.1515/dx-2018-0051
Received July 13, 2018; accepted November 22, 2018; previously published online December 18, 2018

Abstract: Transportation of blood samples is a major part of the preanalytical pathway and can be crucial in delaying laboratory results to the clinicians. A variety of aspects however makes sample transportation a complex, challenging and often overlooked task that needs thorough planning and dedicated resources. The purpose of this review is to outline the options available for this task and to emphasize the preanalytical aspects that need consideration in this process, e.g. performance specifications for sample transportation as stated in ISO standards 15189 and 20658, quality control of automated transportation systems, monitoring of sample integrity parameters and temperature surveillance in general and for external samplers in particular. All these are tasks that the laboratory must assure on a daily basis in terms of continuous quality control, and simultaneously the laboratory must remain alert to alterations in clinical demands (sample frequency, turn-around-times) and new regulations within this area (e.g. the recent General Data Protection Regulation from the EU).

Keywords: preanalytical; sample transportation.

***Corresponding author: Mads Nybo,** MD, PhD, Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Sdr. Boulevard 29, Odense 5000, Denmark, Phone: +45 2055 3952, E-mail: mads.nybo@rsyd.dk
Janne Cadamuro: Department of Laboratory Medicine, Paracelsus Medical University, Salzburg, Austria, E-mail: janne.cadamuro@salk.at
Michael P. Cornes: Department of Clinical Chemistry, Worcestershire Acute Hospitals NHS Trust, Worcester, UK, E-mail: michael.cornes@nhs.net
Rubén Gómez Rioja: Laboratorio Clínico Hospital La Paz, Madrid, Spain, E-mail: rgrioja@salud.madrid.org. https://orcid.org/0000-0002-3429-0427
Kjell Grankvist: Department of Medical Biosciences, Clinical Chemistry, Umeå University, Umeå, Sweden, E-mail: kjell.grankvist@medbio.umu.se

Background

Transportation of blood samples is a major part of the preanalytical pathway and can be crucial in delaying laboratory results to the clinicians [1]. Due to increasing demands from the clinicians, it is important to have the primary venous specimen collection tubes transported to the laboratory as fast as possible to be able to measure analytes within the established stability time [2–7] to maintain fast turnaround times and ensure sample integrity [8, 9]. Furthermore, the transportation process itself must be firmly controlled to assure that the analyses requested are not affected by temperature, agitation, or other physical or biological influences [10]. Finally, transportation logistics must be well arranged to satisfy sample flow from hospital wards as well as, e.g. general practitioners (GPs), while at the same time matching sample reception with the workflow at the laboratory in terms of numbers of samples, peak arrival during daytime, etc. Any delay from blood collection to centrifugation and analysis or any deviation from standard transportation conditions could potentially alter laboratory results and subsequently have a negative impact on patient safety [11]. Of note, the impact of transportation time and conditions on test results is highly dependent on the analytes requested, time to centrifugation as well as on the analytical method applied. Multiple sample stability studies are available for separated as well as whole blood samples, though not necessarily for every analyte [2–7].

All these aspects make sample transportation a complex, challenging and often overlooked task that needs thorough planning and resources taking into account a profound understanding of which preanalytical factors that could alternate the test results. This information has to be cascaded amongst all parties involved in the transportation process (e.g. clinicians, nurses, phlebotomists, carriers, etc.). The purpose of this review is to outline the options available for this task and to emphasize the preanalytical aspects that need consideration in this process.

Regulations

A wide number of regulations and legislations has to be obeyed when biological materials are transported. In

general, regulations that cover transport of dangerous goods by road and rail in Europe are derived from the European agreement concerning the International Carriage of Dangerous Goods by Road (ADR) and Rail (RID) (https://www.unece.org/fileadmin/DAM/trans/danger/publi/adr/adr2017/ADR2017e_web.pdf), or by plane in the International Air Transport Association Dangerous Goods Regulations (https://www.iata.org/whatwedo/cargo/dgr/pages/index.aspx). Overall, these directives implement international agreements governing the transport of dangerous goods, but one must also consult local, national (e.g. [12]) or international governmental material [e.g. from the European Union (https://ec.europa.eu/transport/road_safety/topics/dangerous_goods_en)] on the management of risks in laboratories. From a more laboratory-specific point of view, the requirements stated in the Clinical Laboratory Standards Institute (CLSI) guideline on *Procedures for the handling and processing of blood specimens for common laboratory tests* [13] and the ISO 20658:2017 on Requirements for collection, transport, receipt, and handling of samples [14] should be followed by any accredited laboratory. Of note, the latter standard contains the requirements for sample receipt, and identification and control of non-conformities. How these requirements are best and practically fulfilled need to be carefully considered by each laboratory. Recently, the General Data Protection Regulation from the European Union has set new standards for citizens' data privacy (https://www.eugdpr.org/), which could challenge how sample tubes are labelled at external sampling and also challenge the current in-house transportation of labelled samples. The consequences of this are however still to be seen.

Means of transport

In-house sample transportation

For in-house samples, transportation can be manually or automated:

Manual transportation by trolley or by hand (e.g. by the phlebotomist or the clinician drawing a STAT sample) are both very reliable as no technical instruments are involved and also, it is an accustomed transportation form. It is however slow, and if emergency samples are carried by hand the time spent with sample transportation is time lost to perform other tasks. Another hurdle is the tendency to gather samples at the wards in order to send them in batches to the laboratory. This perhaps saves transportation labour, but the first sample collected may have been waiting for hours at the ward before it is transported to the lab. Also, if samples are received batch-wise, it is not possible to maintain a "first-in-first-out" (FIFO) process, as the laboratory does not know in which order the samples were collected.

As a consequence of these drawbacks, an increasing number of hospitals use automated transportation systems, which can be pneumatic tube transportation systems (PTS) [15] or, e.g. an electric track vehicle [16]. Both fit nicely into automation of the in-house sample reception at the laboratory; it also tends to make the wards send their samples in more "real time", enabling the laboratory to maintain the FIFO principle, and as a natural consequence, it facilitates speed, unidirectional flow and high throughput. However, it also poses obstacles to be addressed by the laboratory professionals: It is important to note that the test request information has to be available at the laboratory when the sample arrives, which makes electronic requisition more flow-efficient than paper requisitions. Separated transport of samples and test request information in terms of paper requisitions leads to further delay in the processing of the ordered analysis, which often leads to resampling and is the cause of laborious tracing efforts for both the wards and the laboratory. Thus, if an automated sample reception system is to work, test requests must be electronically handled. A more basic problem is the obvious risk of processing the serum samples *too* quick, i.e. not allowing time for clot formation before centrifugation. This results in fibrin issues, which can be either interference with a number of analyses or a fibrin clot blocking the sample pipetting needle leading to a false result and possibly "down time" of the analyser – in both instances a new blood sample is needed causing delay in the clinical process. This can be solved by programming a halt in the sample flow for these serum tubes, but one must however first be aware of the problem. Another main issue is the increased risk of haemolysis shown by a number of studies (e.g. [17–19]) and also demonstrated by use of a smart phone [20]. But as revealed by a systematic review there is no general evidence for the safety of using PTS for blood sample transportation [15]. This is mainly due to the high degree of heterogeneity of the retrieved studies, but also because the local, physical PTS arrangement impacts the sample transported in an unpredictable way: Automated PTS are very individually constructed, and conditions concerning the usability (how easy can the samples be loaded?), the g-force impact (due to speed, twist and turns), the actual physical impact on the sample (which along with the mentioned *g* impact also includes bumps of the tubes during "pit stops" during transport and at the

arrival at the laboratory), and finally the temperature (if the PTS goes underground or outside a building) are all parameters that requires a closer scrutiny to assure sample integrity during automated transportation.

So ideally, laboratories must measure and document the *actual* acceleration forces in their existing PTS. For this, use of G-loggers to measure acceleration vector sums has been suggested, and the laboratory should accordingly institute quality target thresholds for these values [10]. Another more simple possibility is the use of daily test results from a particular PTS, where, e.g. median potassium values can be used to monitor changes in the impact on blood samples. Single potassium values will thus *not* have any relevance, while running potassium median values will provide sufficient monitoring; again, the laboratory must establish a target threshold and define what action should be taken if exceeded. Haemolysis index values for each PTS can also be used, but notably, samples *can* be affected without haemolysis, e.g. if potassium leaks from leukocytes or platelets during transportation [21], a preanalytical error that will remain undetected by the haemolysis index. A significant preanalytical effect on samples transported by PTS has for instance been noted for thromboelastographic analyses. For these analyses, manual transport of samples is therefore recommended [22], and in the case of platelet function testing best practice is to avoid any transportation at all and if possible, perform the blood collection at the test site.

In order to continuously minimize turnaround times in all clinical settings, a forthcoming challenge will be the use of automated PTS for all different kinds of sample materials, e.g. paediatric samples, urine, cerebrospinal fluid [23], free DNA measurement [24], culture media and even pathology specimens [25].

External sample transportation (from general practitioners or external laboratories)

External samples are transported in a variety of ways, e.g. by car [26], in boxes [27], using drones [28, 29], or even by planes and trains. If the samples are properly protected from temperature deviation and agitation, none of these transportation forms should affect the samples significantly [10]. It is however crucial to monitor these conditions – and also a demand according to the ISO15189 accreditation that most laboratories carry.

The transportation of venous blood samples from outside the hospital setting is often costly and logistically challenging. Flaws in tube labelling, packaging and transport cause delays and increased costs with several stakeholders involved. The transportation routines should be described and agreed upon, also including what to do when these routines are deviated from. A number of technical support systems for this, including software [30] and intelligent transportation boxes with GPS and temperature loggers [31], are already on the market, and such features will for certain be an important part of an improved preanalytical quality assurance in the future.

Transport control systems

Optimally, transportation should be performed under the same temperature conditions as storage before and after analysis until the analysis quality control has been performed and approved. Ideally, the time and temperature of transport boxes should be logged, which previously has been nicely described [10]. At best, temperature data from the transportation phase should be incorporated in the laboratory information system (LIS) in order to facilitate a swift, automated approval procedure when receiving outhouse samples. Such systems are not yet available, but LIS companies should be encouraged to develop such functionalities.

There is a large body of evidence on sample stability (e.g. [32–34]), but specification and documentation of sample stability under different circumstances and ambient temperatures are outside the scope of this review; to retrieve this information the reader could consult e.g. *Tietz' textbook* [35] or Guder's *Diagnostic Samples* [2]. But in order to judge stability of the analytes, information on specimen collection time, time to centrifugation and analysis time are inevitable and must be presented in the LIS. Samples that are not guaranteed to reach the laboratory the same day must be centrifuged, which necessitates centrifugation capability and educated personnel, e.g. at the GP. This however requires quality assurance of the centrifugation performed as well as of sample aliquoting (if performed). Therefore, sampling of specimens for analytes with short-time stability or demanding storage in plain tubes after centrifugation or freezing prior to transport must be specified in the laboratory's specimen collection guidelines, which according to the ISO15189 must be distributed to external samplers. Just as samples are rejected due to haemolysis, samples with analytes beyond the specified stability time and outside the approved temperature limits should be rejected for analysis. Importantly, routines should be established at the laboratory to avoid similar situations in the future.

Third party delivery

Security systems must be established that ensures sample transportation by a third party if such are used, e.g. samples send by mail: Although used widely in many countries, the efficiency of postal systems is generally deteriorating due to the now-a-days more IT-dependent communication, and one must therefore assure sample integrity if postal delivery is delayed. This is, e.g. a problem with centralised investigations such as screening for colorectal cancer using immunochemical testing of faecal occult blood (iFOBT), where samples are sent by public postal delivery. A recent study with stability tests of faeces samples stored at 30°C for 14 days showed no change in the distribution of iFOBT tests below and above the cut-off [36], and the significantly delayed sample delivery was therefore not an issue. Such developments can be foreseen for a variety of samples and analytes, and it is of course the responsibility of the laboratory to monitor and if necessary, validate any alterations in a third party transport that could affect sample integrity.

Conclusions

Although automation of the laboratory tends to ease a number of (especially) preanalytical issues, there is still a vast amount of challenges to deal with. Regarding sample transportation, all laboratories must establish performance specifications for sample transportation as stated in ISO standards 15189 and 20658. In an ideal world, the preanalytical conditions during transportation are specified for all types of specimens, and as a minimum this should include maximum time of transportation, recommended temperature range, and also specify the most usual exceptions in terms of, e.g. short-time stability, susceptibility to transport, agitation and processing. Also, automation systems, e.g. PTS, must be quality-assessed, not only prior to use, but also continuously to assure sample integrity. Other sample integrity parameters to be monitored are of course haemolysis and clotting, but also stability and temperature parameters for the specific analytes must be followed. For the latter, temperature surveillance must be installed with pre-specified acceptance limits, and at best the LIS should be used to handle these data; if necessary, the suppliers must be urged to develop these possibilities. Altogether, the laboratory must be aware of its responsibility of continuous quality control of the *entire* transportation process, including delivery circumstances for third party deliverers, while simultaneously remain alert to alterations in clinical demands (sample frequency, turnaround times) and new regulations within this area.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organisation(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Lippi G, Chance JJ, Church S, Dazzi P, Fontana R, Giavarina D, et al. Preanalytical quality improvement: from dream to reality. Clin Chem Lab Med 2011;49:1113–26.
2. Guder WG, Narayanan S, Wisser H, Zawta B. Diagnostic samples: from the patient to the laboratory, 4th ed. Darmstadt: GIT-Verlag; Weinheim: Wiley-Blackwell, 1996, 2009.
3. Dupuy AM, Cristol JP, Vincent B, Bargnoux AS, Mendes M, Philibert P, et al. Stability of routine biochemical analytes in whole blood and plasma/serum: focus on potassium stability from lithium heparin. Clin Chem Lab Med 2018;56:413–21.
4. Henriksen LO, Faber NR, Moller MF, Nexo E, Hansen AB. Stability of 35 biochemical and immunological routine tests after 10 hours storage and transport of human whole blood at 21 degrees C. Scand J Clin Lab Invest 2014;74:603–10.
5. Monneret D, Godmer A, Le Guen R, Bravetti C, Emeraud C, Marteau A, et al. Stability of routine biochemical analytes in whole blood and plasma from lithium heparin gel tubes during 6-hr storage. J Clin Lab Anal 2016;30:602–9.
6. Oddoze C, Lombard E, Portugal H. Stability study of 81 analytes in human whole blood, in serum and in plasma. Clin Biochem 2012;45:464–9.
7. Leino A, Koivula MK. Stability of chemical and immunochemical analytes in uncentrifuged plasma samples. Ann Clin Biochem 2009;46:159–61.
8. Grasas A, Ramalhinho H, Pessoa LS, Resende MG, Caballé I, Barba N. On the improvement of blood sample collection at clinical laboratories. BMC Health Serv Res 2014;14:12.
9. Jørgensen P, Jacobsen P, Poulsen JH. Identifying the potential of changes to blood sample logistics using simulation. Scand J Clin Lab Invest 2013;73:279–85.
10. Zaninotto M, Tasinato A, Padoan A, Vecchiato G, Pinato A, Sciacovelli L, et al. An integrated system for monitoring the quality of sample transportation. Clin Biochem 2012;45:688–90.
11. Green SF. The cost of poor blood specimen quality and errors in preanalytical processes. Clin Biochem 2013;46:1175–9.
12. Biological agents: managing the risks in laboratories and healthcare premises. Advisory Committee on Dangerous Pathogens, Health and Safety Executive, UK, 05/2005.

13. Clinical Laboratory Standards Institute (CLSI). Procedures for the handling and processing of blood specimens for common laboratory tests, 4th ed. CLSI Standards GP44-A4. Wayne, PA: Clin. Lab. Stand. Inst, 2010.
14. International Standards Organisation. ISO/TS 20658:2017 Medical laboratories – requirements for collection, transport, receipt, and handling of samples. Geneva, Switzerland: International Organization for Standardization, 2012.
15. Nybo M, Lund ME, Titlestad K, Maegaard CU. Blood sample transportation by pneumatic transportation systems: a systematic literature review. Clin Chem 2018;64:782–90.
16. Lou AH, Elnenaei MO, Sadek I, Thompson S, Crocker BD, Nassar BA. Multiple pre- and post-analytical lean approaches to the improvement of the laboratory turnaround time in a large core laboratory. Clin Biochem 2017;50:864–9.
17. Gomez-Rioja R, Fernandez-Calle P, Alcaide MJ, Madero R, Oliver P, Iturzaeta JM, et al. Interindividual variability of hemolysis in plasma samples during pneumatic tube system transport. Clin Chem Lab Med 2013;51:e231–3.
18. Böckel-Frohnhöfer N, Hübner U, Hummel B, Geisel J. Pneumatic tube-transported blood samples in lithium heparinate gel separator tubes may be more susceptible to haemolysis than blood samples in serum tubes. Scand J Clin Lab Invest 2014;74:599–602.
19. Sodi R, Darn SM, Stott A. Pneumatic tube system induced haemolysis: assessing sample type susceptibility to haemolysis. Ann Clin Biochem 2004;41:237–40.
20. Mullins GR, Harrison JH, Bruns DE. Smartphone monitoring of pneumatic tube system-induced sample hemolysis. Clin Chim Acta 2016;462:1–5.
21. Šálek T. Pseudohyperkalemia – Potassium released from cells due to clotting and centrifugation – a case report. Biochem Med 2018;28:011002.
22. Wallin O, Söderberg J, Grankvist K, Jonsson PA, Hultdin J. Preanalytical effects of pneumatic tube transport on routine haematology, coagulation parameters, platelet function and global coagulation. Clin Chem Lab Med 2008;46:1443–9.
23. Imoh LC, Mutale M, Parker CT, Erasmus RT, Zemlin AE. Laboratory-based clinical audit as a tool for continual improvement: an example from CSF chemistry turnaround time audit in a South-African teaching hospital. Biochem Med (Zagreb) 2016;26:194–201.
24. Kriegshäuser G, Wagner C, Mangge H, Halwachs-Baumann G, Enko D. Impact of pneumatic tube system transport of whole blood samples on free DNA concentration in human plasma. Clin Chem 2016;62:1672–3.
25. Metovic J, Bertero L, Musuraca C, Veneziano F, Annaratone L, Mariani S, et al. Safe transportation of formalin-fixed liquid-free pathology specimens. Virchows Arch 2018;473:105–13.
26. Felding P, Petersen PH, Hørder M. The stability of blood, plasma and serum constituents during simulated transport. Scand J Clin Lab Invest 1981;41:35–40.
27. Lippi G, Lima-Oliveira G, Nazer SC, Moreira ML, Souza RF, Salvagno GL, et al. Suitability of a transport box for blood sample shipment over a long period. Clin Biochem 2011;44:1028–9.
28. Amukele TK, Hernandez J, Snozek CL, Wyatt RG, Douglas M, Amini R, et al. Drone transport of chemistry and hematology samples over long distances. Am J Clin Pathol 2017;148:427–35.
29. Amukele TK, Sokoll LJ, Pepper D, Howard DP, Street J. Can unmanned aerial systems (drones) be used for the routine transport of chemistry, hematology, and coagulation laboratory specimens? PLoS One 2015;10:e0134020.
30. Lippi G, Sciacovelli L, Simundic AM, Plebani M. Innovative software for recording preanalytical errors in accord with the IFCC quality indicators. Clin Chem Lab Med 2017;55:e51–3.
31. Zaninotto M, Tasinato A, Vecchiato G, Legnaro A, Pinato A, Plebani M. Performance specifications in extra-analytical phase of laboratory testing: sample handling and transportation. Clin Biochem 2017;50:574–8.
32. Jensen EA, Stahl M, Brandslund I, Grinsted P. Stability of heparin blood samples during transport based on defined pre-analytical quality goals. Clin Chem Lab Med 2008;46:225–34.
33. Stahl M, Brandslund I. Controlled storage conditions prolong stability of biochemical components in whole blood. Clin Chem Lab Med 2005;43:210–5.
34. Gómez Rioja R, Martínez Espartosa D, Segovia M, Ibarz M, Llopis MA, Bauça JM, et al. Laboratory sample stability. Is it possible to define a consensus stability function? An example of five blood magnitudes. Clin Chem Lab Med 2018;56:1806–18.
35. Rifai N, Horvath AR, Wittwer CT, editors. Tietz' textbook of clinical chemistry and molecular diagnostics, 6th ed. St. Louis, MO: Elsevier, 2018.
36. Hansen AT, Hoffmann-Lücke E, Nielsen BK, Reinholdt B, Hindersson P, Heidemann K, et al. Delayed sample arrival at the laboratory does not lead to more false negatives in the Danish population screening for colorectal cancer. Scand J Clin Lab Invest 2017;77:685–8.