Quality of Diagnostic Samples

Recommendations of the Working Group on Preanalytical Quality of the German Society for Clinical Chemistry and Laboratory Medicine

W.G.Guder, F. da Fonseca-Wollheim, W. Heil, Y. Schmitt, G. Töpfer, H. Wisser , B. Zawta (†)

Corresponding members and industry representatives :

Carmen Alt, Recipe Chemicals and Instruments, Munich, Germany

G. Banfi, Milan, Italy

K. Bauer, Vienna, Austria

W. Brand, Sarstedt, Nümbrecht, Germany

M. Buchberger, C.A. Greiner, Krems-münster, Austria

S. Church, BD Diagnostics, Europe, Oxford, England

A. Deom, Geneva, Switzerland

V. Ehrhardt, Roche Diagnostics GmbH, Mannheim, Germany

G.M. Fiedler, Leipzig, Germany

C.G. Fraser, Dundee, Scotland

S. Golf, Giessen,Germany

H. Gross, Kendro Laboratory Products, Hanau, Germany

G. Gunzer, Beckmann-Coulter, Olym-pus, Munich, Germany

P. Hagemann, Zürich, Switzerland

H. Hallander, Solna, Sweden

N. Hamasaki, Fukuoka, Japan

J. Henny, Vandoeuvre - lès - Nancy, France

R. Hinzmann, Sysmex-Europe, Norderstedt, Germany

G. Hoffmann, Trillium, Grafrath, Germany

P. Hyltoft Petersen, Odense, Denmark

A. Kallner, Stockholm, Sweden

H. Kitta, Klinika GmbH, Usingen, Germany

Daniela Klahr, Andreas Hettich GmbH, Tuttlingen, Germany

D. Kolpe, Kabe Labortechnik GmbH, Nümbrecht-Elsenroth, Germany

J. Kukuk, Rolf Greiner Biochemica, Limburg, Germany

Tamara Kunert-Latus, Terumo Europe, Leuven, Belgium NV

M. Lammers, Patrizia Mikulcik, Siemens Healthcare Diagnostics, Marburg and Eschborn, Germany

E.A. Leppänen, Helsinki, Finland

S. Naryanan, New York, USA

M. Neumaier, Mannheim, Germany

Maria Adelina Peça Gomes, Lisbon, Portugal

K.-H. Pick, Abbott GmbH, Wiesbaden, Germany

Antje Piening, Beckmann-Coulter, Nyon, Switzerland

R. Probst, Olching, Germany

Elke Rauhut, DiaSorin, Dietzenbach, Germany

Carmen Ricos, Barcelona, Spain

Kathrin Schlüter, BD Diagnostics, Heidelberg, Germany

O. Sonntag, Ortho Clinical Diagnostics, Neckargemünd, Germany

D. Young, Philadelphia, USA

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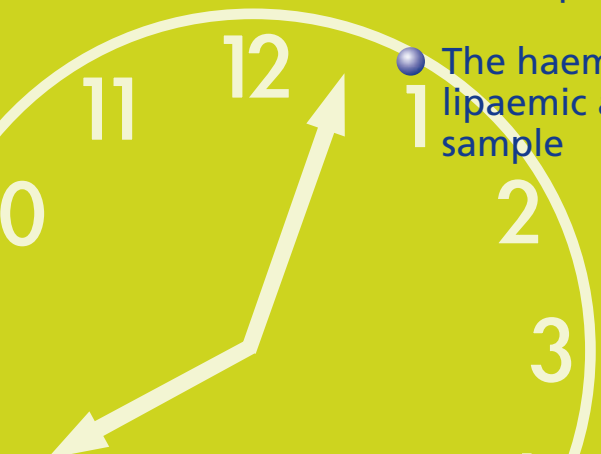
BD

Helping all people live healthy lives

- Plasma, serum or whole blood?
- Choice of anticoagulant
- The optimal sample volume
- Stability during transport and storage of samples
- The haemolytic, lipaemic and icteric sample



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1. Introduction

It is imperative that the in vivo state of a constituent remains unchanged after withdrawal of the body fluid from a patient to obtain a valid medical laboratory result. This may not always be possible when measuring extracellular and cellular components of blood. Platelets and coagulation factors are activated when blood vessels are punctured, and their activation continues in sample containers that do not contain anticoagulant.

Historically, serum was the preferred assay material for determining extracellular concentrations of constituents in blood. Today, plasma is preferred for many, but not all laboratory investigations because the constituents in plasma are better at reflecting the pathological situation of a patient than those in serum. Some changes of constituents can be avoided by using anticoagulants. The types and concentrations of anticoagulants used in venous blood samples were defined in the international standard (117) in 1996. The standardised anticoagulants are now used to prepare standardised plasma samples for laboratory investigations throughout the world.

This document summarises the findings published in the literature and those observed by the contributors on the use of anticoagulants. The overview was prepared in collaboration with experts from clinical diagnostic laboratories and the diagnostics industry (94-97), recently published in German in its 6th edition (98).

In the meantime, this work was confirmed by several international publications. After Bonini et al. (25) concluded from the existing literature that 50 -75 % of laboratory errors appear in the preanalytical phase, this part of medical laboratory became increasingly important in literature and daily practice. Thus Fiedler and Thiery (67,252) showed that interpretation of laboratory results leads to false conclusions due to preanalytical errors. Contributions to the preanalytical phase to results in coagulation testing (20, 174), tumor marker diagnostics (4), cardiac markers (17) and therapeutic drug monitoring (244) express the importance of including this phase in quality assurance programmes. Experience during laboratory accreditation procedures also confirmed the importance which has been included into the ISO EN, DIN standard 15 189 on quality and competence requirements in medical laboratories (118).

This standard includes requirements and advice regarding preanalytical quality under chapter

5.4 : Pre examination procedures

5.4.1 The request form shall contain information sufficient to identify the patient and the authorised requester, as well as providing pertinent clinical data. National, regional or local requirements shall apply.

The request form, or an electronic equivalent, should allow space for the inclusion of, but not be limited to, the following:

- unique identification of the patient ;
- name or other unique identifier of physicians or other persons legally authorised to request examinations or use medical information together with the destination for the report. The requesting clinician´s address should be provided as part of the request form information when it is different from that of the receiving laboratory.
- type of primary sample and the anatomic site of origin, where appropiate;
- examinations requested;
- clinical information relevant to the patient, which should include gender and date of birth, as a minimum, for interpretation purposes;
- date and time of primary sample collection;
- date and time of receipt of samples by the laboratory.

5.4.2 Specific instructions for the proper collection and handling of primary samples shall be documented and implemented by laboratory management and made available to those responsible for primary sample collection. These instructions shall be contained in a primary sample collection manual.

5.4.3 The primary sample collection manual shall include the following:

a) Copies or refences to
- lists of available laboratory examinations offered,
- consent forms, when applicable,
- informations and instructions provided to patients in relation to their own preparation before primary sample collection, and
- information for users of laboratory services on medical indications and appropriate selection of available procedures;

b) Procedures for:
- preparation of the patient (e.g. instructions to care givers and phlebotomists),
- identification of primary sample, and
- primary sample collection (e.g. phlebotomy, skin puncture, blood, urine and other body fluids), with description of the primary sample containers and necessary additives;

c) Instructions for
- completion of request form or electronic request,
- type and amount of primary sample to be collected;
- special timing of collection, if required,
- any special handling needs between time of collection and time received by the laboratory(transport requirements, refrigeration, warming, immediate delivery etc.),
- labelling of primary samples,
- clinical information (e.g. history of administration of drugs) ,
- positive identification, in detail, of the patient from whom the primary sample is collected,

- recording the identity of the person collecting the primary sample,
- safe disposal of materials used in the collection;

d) Instructions for
- storage of examined samples ,
- time limits for requesting additional examination,
- additional examinations, and,
- repeat examinations due to analytical failure or further examinations of same primary sample".

The following texts describe detailed advice regarding transport and storage of primary tubes:

5.4.14: Samples shall be stored for a specified time, under conditions ensuring stability of sample properties, to enable repetition of the examination after reporting of the results or for additional examinations."

These processes have become part of national and international quality management and -assurance procedures and are increasingly used during certification and accreditation procedures. They became part of the directives of the Federal Medical Association (Bundesärztekammer) in 2008 (204).

The authors hope that the included recommendations developed over many years can contribute to the improvement of medical laboratory results and thereby help provide patients with better treatment.

2. Serum, Plasma or Whole Blood? Which Anticoagulants to Use?

2.1 Definitions

Whole blood
A venous, arterial or capillary blood sample in which the concentrations and properties of cellular and extracellular constituents remain relatively unaltered when compared with their in vivo state. Anticoagulation in vitro stabilises the constituents in a whole blood sample for a certain period of time.

Plasma
The virtually cell-free supernatant of blood containing anticoagulant obtained after centrifugation.

Serum
The undiluted, extracellular portion of blood after adequate coagulation is complete.

Anticoagulants
Additives that inhibit blood and/or plasma from clotting to ensure that the constituents to be measured are not significantly changed prior to the analytical process. Anticoagulation occurs by binding calcium ions (EDTA, citrate) or by inhibiting thrombin activity (heparinates, hirudin). The following solid or liquid anticoagulants are mixed with blood immediately during sample collection:

EDTA
Salts of ethylene diamine tetraacetic acid. Dipotassium (K_2), tripotassium (K_3) and disodium (Na_2) salts are used (13, 87, 117); concentrations: 1.2 to 2.0 mg/mL blood (4.1 to 6.8 mmol/L blood) based on anhydrous EDTA. The ICSH recommends K_2-EDTA for haematological investigations (115).

Citrate
Trisodium citrate with 0.100 to 0.136 mol/L citric acid. Buffered citrate with pH 5.5 to 5.6: 84 mmol/L trisodium citrate with 21 mmol/L citric acid. 0,109 mol/L (3,2%) was recommended to reach international standardisation (38,117). Because differences were noticed between 3.2% and 3.8% (v/v) citrate when reporting results in INR (1, 38,281), WHO and CLSI recommend 0.109 mol/L (3.2%) citric acid (38,117).

A mixture of one part citrate with nine parts blood is recommended for coagulation tests (38, 117).
One part citrate mixed with four parts blood is recommended to determine the erythrocyte sedimentation rate (117).

Heparinates
12 to 30 IU/mL of unfractionated sodium, lithium or ammonium salt of heparin with a molecular mass of 3 to 30 kD is recommended to obtain standardised heparinised plasma (117).

Calcium-titrated heparin at a concentration of 40 to 60 IU/mL blood (dry heparinisation) and 8 to 12 IU/mL blood (liquid heparinisation) is recommended for the determination of ionized calcium (24, 29). Similar recommendations exist regarding ionized magnesium (21).

Hirudin
Hirudin is an antithrombin extracted from leeches or prepared by a genetic engineering process. Hirudin inhibits thrombin by forming a 1:1 hirudin-thrombin complex. Hirudin is used at a concentration of 10 mg/L (58). It was tested to replace other anticoagulants as universal anticoagulant (169).

The **colour codes** of anticoagulants are presently not standardised:
EDTA = lavender or red;
citrate 9 + 1 = light blue or green;
citrate 4 + 1 = black or mauve;
heparinate = green or orange;
no additives (for serum) = red or white.
Additional colours are used for different additives (e.g. grey for glycolysis inhibitors) such as CTAD (citrate, theophylline, adenosine, dipyramidol) and separator gels. This is to be considered when tubes from different producers are used.

2.2 Plasma or serum?

Advantages of using plasma
The following aspects support the preferential use of plasma versus serum in laboratory medicine:

Time saving: Plasma samples can be centrifuged directly after sample collection, unlike serum, in which coagulation is completed after 30 minutes,
Higher yield: 15 to 20 % more in volume of plasma than of serum can be isolated from the same volume of blood.
Prevention of coagulation-induced interferences: Coagulation in primary and secondary tubes that were already centrifuged, may block suction needles of the analysers when serum tubes are used. This is prevented by using anticoagulants.

Prevention of coagulation-induced influences: The coagulation process changes the concentrations of numerous constituents of the extracellular fluid beyond their maximum allowable limit (99, 271). The changes are induced by the

following mechanisms:

a. Increase in the concentrations of platelet components in serum as compared to plasma (e.g. potassium, phosphate, magnesium, aspartate aminotransferase, lactate dehydrogenase, serotonin, neurone-specific enolase, zinc). Release of amide-NH3 from fibrinogen induced by action of clotting factor XIII.
b. Decrease in the concentration of constituents in serum as a result of cellular metabolism and the coagulation process (glucose, total protein, platelets).
c. Activation of the cell lysis of erythrocytes and leukocytes in non-coagulated blood (cell-free haemoglobin, cytokines, receptors).

Certain constituents should only be measured in plasma (e.g. neurone-specific enolase, serotonin, ammonia) to obtain clinically relevant results.

Disadvantages of plasma over serum

The addition of anticoagulants may interfere with certain analytical methods or change the concentration of the constituents to be measured:

a. Contamination with cations: NH_4^+, Li^+, Na^+, K^+.
b. Assay interference caused by metals complexing with EDTA and citrate (e.g. inhibition of alkaline phosphatase activity by zinc binding, inhibition of metallo-proteinases, inhibition of metal-dependent cell activation in function tests, binding of calcium (ionized) to heparin (24)).
c. Interference by fibrinogen in heterogeneous immunoassays (271).
d. Inhibition of metabolic or catalytic reactions by heparin: e.g., Taq polymerase in the polymerase chain reaction (PCR) (181).
e. Interference in the distribution of ions between the intracellular and extracellular space (e.g. Cl^-, NH_4^+) by EDTA, citrate (99).
f. Serum electrophoresis can be performed only after pre-treatment to induce coagulation in plasma.

2.3 Recommendations

Table 6.1 indicates sample types that are recommended for a specific test. The table also contains information on the utility of other sample materials as long as the results measured by that method do not exceed the maximum allowable deviation of measurement (204) as defined by the biological variation (205). A maximum deviation of 10 % is assumed as being acceptable for a constituent if deviation of measurement is not defined (58).

Sample collection and transport time

The following sequence for filling tubes with blood from a patient is recommended to avoid contamination (99), modified for plastic tubes in 2007 (40):

1. blood for blood culture,
2. citrate 1+ 9 for coagulation tests,

2a. citrate 1+ 4 for blood sedimentation rate,

3. serum tube with no additive (avoid serum as first tube when electrolytes will be measured (154)),

3a. serum with gel and/or coagulation activator,

4. heparinate – plasma tube without gel separator,

4a. heparinate- plasma with gel separator tube,

5. EDTA tubes for haematology tests,
6. tubes containing additional stabilisers (e.g. glycolytic inhibitors),
7. trace element tube and other special tubes.

Only the recommended quantity of anticoagulant should be added, wherever required, to avoid errors in results.

Tilt the tube repeatedly (3-4 times with citrate, 5-6 times with serum, 8-10 times with sedimentation rate, heparinate and other tubes, do not shake and avoid foaming) immediately after filling to mix the sample thoroughly with the anticoagulant. Leave the containers at room temperature for at least 30 minutes to separate serum from blood cells in blood that was taken from non-anticoagulated patients. This period is shorter when coagulation has been activated. Leave the sample at room temperature no longer than the period indicated in the table (see 6.1).

Centrifugation

Blood cells are rapidly separated from plasma/serum by centrifugation at increased relative centrifugal force (rcf). Rcf and rotations per minute (rpm) are calculated using the rotating radius r (the distance between the axis of rotation and the base of the container in mm) by the following equation:

$$rcf = 1{,}118 \times r\ (rpm/1000)^2$$

Centrifuge blood containers in 90°-swing-out rotors so that the sediment surface forms a right angle with the container wall. This helps to prevent contact between the sampling needle and the surface of the cell layer or separating gel in the tube, when the centrifuged blood containers are directly transferred to an analyser for analysis.When plasma coagulation is complete, centrifuge the sample for at least 10 minutes at a minimum relative centrifugal force of 1500 *g*.

Centrifuge the anticoagulated blood (citrated, EDTA or heparinised blood) for at least 15 minutes at 2000 to 3000 *g* to obtain cell-free plasma (99).

When separating serum or plasma, the temperature should not drop below 15 °C or exceed 24 °C.

Storage

Non-centrifuged samples should be stored at room temperature for the time specified in the recommendations for stability (see table 6.1). After centrifugation, the serum or plasma should be analysed within the time as recommended for whole blood, if the sample is stored without using a separating gel (82) or a filter separator in primary tubes. When the sample will be refrigerated or frozen for preservation, blood cells must first be separated from serum or plasma. Do not freeze whole blood samples before or after centrifugation, even when polymer separating gels are used.

Evaluation of new analytical procedures

Before using a new reagent or method, examine the suitability of the procedure by comparing the results of at least 20 blood samples with normal, and 20 with pathological concentrations of the constituent to be measured. The criteria for biological and clinical interpretation (reference intervals, clinical decision limits) may have to be changed, if the mean of the difference between the samples tested deviates by more than the maximum deviation allowed (204) (alternatively by more than 10 %).

3. The Optimal Sample Volume

The progress in the development of laboratory analysers has led to a reduction of the sample volume for analysis. The development, however, is not necessarily accompanied by an adaptation of sample tubes and therefore often excessive sample volumes are collected. Studies revealed (46) that 208 mL blood for 42 tests is taken during an average stay of a patient in a department of internal medicine. In intensive care the total volume drawn for 125 tests was 550 mL of blood. Previous publications describe that in half of the patients who received blood transfusion, more than 180 mL of blood were taken for laboratory tests (235). "Iatrogenic anaemia" caused by excessive blood sampling is a well-known phenomenon in paediatrics (52), whereas iatrogenic anaemia is hardly recognized as an important phenomenon in the acute and intensive care of adult patients. The following recommendations were made for sampling reduced blood volumes for analysis (95):

3.1 Definition

The amount of sample needed for laboratory diagnostic purposes (Vol b) is defined by:

1. The analytical sample volume (Vol a),
2. The dead-space volume of the analyser (Da), measured as mL plasma/serum,
3. The dead-space volume of the primary sample tube (Dp), measured as mL blood,
4. The dead-space volume of secondary sample tubes (Ds), measured as mL plasma/serum,
5. The amount of sample needed for the number (N) of repetitive analyses and additional follow-up tests,
6. The plasma sample yield according to the respective haematocrit.

Assuming that plasma/serum yield is 50 % of blood volume the total blood needed can be calculated as follows:

Vol b = 2 x (N x (Vol a + Da) + Ds) + Dp

3.2 Recommendations

Assuming a haematocrit of 0.50 and a need for a repetition and follow-up of laboratory tests, four times the analytical sample volume can be considered to be sufficient when plasma or serum will be used. The following standard blood volumes are recommended for analysis using advanced analytical systems. These volumes may be sufficient in 95 % of cases to provide the laboratory results as requested:

— Clinical chemistry: 4 – 5 mL (when using heparin plasma: 3 – 4 mL)
— Haematology: 2 – 3 mL EDTA blood
— Coagulation tests: 2 – 3 mL citrated blood
— Immunoassays including proteins etc: 1 mL whole blood for 3 – 4 immunoassays
— Erythrocyte sedimentation rate: 2 – 3 mL citrated blood
— Blood gases: capillary sampling: 50 µl, arterial or venous sampling: 1 mL heparin blood

The request form for laboratory analyses should include clear information on the required sample volumes and tubes. Tubes of uniform size with different filling volumes should be used. The length of the tubes should be at least four times the tube diameter. These criteria are met by standard tubes of 13 x 75 mm (diameter x length).

3.3 Measures which can help to reduce the required blood volume

— Introduction of primary tube reading in analyzers
— Deletion of sample distribution into secondary tubes
— Use of tubes with smaller diameter
— Use of analysers requiring a smaller analytical sample volume
— Storage of samples in primary tubes, using separators for plasma or serum
— Use of plasma instead of serum

3.4 Documentation

1. Any method description should include the required analytical sample volume.
2. A quality manual should document the requested sample volumes and their handling procedure.
3. The manual should describe the procedures on how to handle patient samples that have an insufficient sample volume.

It is to be expected, that by following these recommendations, together with optimal organization and collaboration with all sending persons, the size of samples can be significantly reduced. In a publication by Wisser et al (280) the real blood loss per patient following these recommendations was reported for 8 different medical disciplines. The following table summarizes the data obtained during a complete hospital stay:

Medical Department	Patient number	total blood loss (mL)	blood loss per day (mL)	number of blood drawings	number of tests ordered	blood loss during intensive care treatment (mL)
Visceral surgery	473	23 (150)	4 (11)	6 (44)	11 (66)	63
Gynecology/ obstetrics	337/180	16 (56)	3 (10)	4 (16)	5 (20)	
Cardiovascular surgery	175	201 (615)	66 (178)	66 (178)	84 (219)	144
Internal medizine	65					29
Gastro-enterology	325	23 (107)	4 (10)	6 (32)	16 (56)	
Nephrology	221	29 (150)	4 (12)	8 (41)	21(70)	
Oncology	416	15 (104)	3 (10)	4 (27)	15 (50)	
Cardiology	527	10 (78)	5 (9)	4 (20)	12 (40)	

Table 1: *Blood loss during hospital stay caused by laboratory tests in eight different clinical disciplines. The numbers give medians with the 95 percentiles in brackets (according to 280)*

When using the tube sizes recommended the lab subspecies used up the following percentages of total blood loss (median): haematology 26 %, coagulation: 17 %, clinical chemistry 45 %, other tests 11 %. The authors reported that only 5 % of patients had a blood loss of > 196 mL, much less than reported in literature. They recommend giving a weekly report to the users of the laboratory on the volumes sent from each patient (280).

4. Analyte Stability in Sample Matrix

The aim of a quantitative laboratory investigation is to determine the concentration or activity of a diagnostically relevant analyte in a body fluid in order to provide information on the clinical situation of a patient. This implies that the composition of the samples for analysis must not change during the preanalytical phase (sampling, transportation, storage, sample preparation).

4.1 Stability and Instability

Stability is the capability of a sample material to retain the initial property of a measured constituent for a period of time within specified limits when the sample is stored under defined conditions (119).

The measure of the instability is described as an absolute difference, as a quotient or as a percentage deviation of results obtained from measurement at time 0 and after a given period of time.

Example:
The transportation of whole blood for 3 to 4 hours at room temperature increases the concentration of potassium from 4.2 mmol/L to 4.6 mmol/L.

Absolute difference:	0,4 mmol/L
Quotient:	= 1,095
Percent deviation:	+ 9,5%

The maximum permissible instability is the deviation of a result that corresponds to the maximum permissible relative imprecision of the measurement. This was defined as 1/12th of the biological reference interval (204). The deviation should be smaller than half of the total error derived from the sum of biological and technical variability (74, 205). The stability of a blood sample during the preanalytical phase is defined by the temperature, the mechanical load in addition to other factors. As time has also a major influence, the stability is stated as the maximum permissible storage time under defined conditions.

The maximum permissible storage time is the period of time at which the stability requirement of 95 % of the samples is met. This is a minimum requirement, since under pathological conditions the stability of a constituent in the sample can be considerably reduced (see examples in 6. Table).

The storage time is stated in suitable units of time (days, hours, minutes). A clear distinction must be made between the storage of the primary sample (blood, urine, cerebrospinal fluid) and the storage of the analytical sample (e.g. plasma, serum, sediment, blood smear). The storage times are adopted for:

1. Storage of the primary sample at room temperature (20 to 25 °C).
2. Storage of the analytical sample at room temperature (20 to 25 °C), refrigerator temperature (4 to 8 °C) and deep-frozen (-20 °C).

4.2 Quality assurance of the time delay during the preanalytical phase

Transport time
The transport time is the difference between the blood sampling time (in general with an accuracy of at least a quarter of an hour) and the registration time of the request and/or the arrival of the sample at the laboratory. The transportation time for each sample should be documented by the laboratory.

Preanalytical time in the laboratory
The preanalytical time in the laboratory is the difference between the time of analysis and the registration time of the sample. When the time at the end of the analytical phase (i.e. printing time of the result) is noted, the analysis time stated in the description of the method must be subtracted.

Documentation
It is recommended to state the sampling time and the arrival time of the sample in the laboratory in the report for the documentation of the transport time.

Actions to be taken when the maximum permissible preanalytical times are exceeded
A medically relevant change to the results must be considered when the maximum permissible transport and preanalytical time of the sample has been exceeded. The laboratory has the responsibility to mark the results of such samples with a note in the report, or to refuse to carry out the test. The latter decision is advisable when medical conclusions may be derived from the result that may be detrimental to the patient. The following example illustrates the problem:

> An EDTA blood sample shows a rise in monocyte number from 4 to 10 % after four hours of storage, measured by an automatic cell counter system. When this result is reported without comment, it could lead to an erroneous medical diagnosis that the patient suffers from a viral infection. Therefore, the clinician should be informed with a comment or a refusal, such as:
>
> *Comment:* "The monocyte count may give incorrectly high values with the method used in our laboratory when EDTA blood is stored more than 2 hours. A control in the smear resulted in normal monocyte counts."

Refusal: "The maximum permissible transportation time was exceeded. Therefore the monocyte results are not stated, because they cannot correctly be determined. For the determination of correct monocyte counts, a maximum transportation time of two hours is acceptable."

5. The Haemolytic, Icteric and Lipaemic Sample

Medical laboratory tests are affected by endogenous and exogenous factors in the sample matrix. Certain potentially interfering factors may be recognised by a coloured appearance of the sample, whereas other factors (e.g. drugs) are detected only by additional information and/or direct analysis. Reference books provide useful information on drug interferences in laboratory analysis (262, 288). Publications of standard setting organisations describe the methodology and statistical methods for the recognition and quantitative estimation of interferences in clinical chemical investigations (39, 85, 86, 239).

It is difficult to predict the effects of haemolysis, turbidity (lipaemia) and bilirubin (icterus), especially when reagents and analytical systems undergo modification (39, 74, 239). This document provides information that the laboratory can consider as appropriate actions to ensure that the results of measurement are clinically relevant.

5.1 Definition of a clinically relevant interference

The maximal allowable deviation (bias) is expressed in % deviation of the result without interference as determined by a reference method. A clinically relevant bias should be considered if the change of the result caused by the interfering substance is more than the maximal allowable deviation of the analytical procedure (204). The bias usually amounts to 1/12 (which is about 8%) of the reference interval.

Data on the biological variability was published to define the medical needs (205). The desirable bias (B) derived from intra-individual (CV_w) and inter-individual (CV_b) variation was established for 316 analytes (205).

Example:
A result for plasma creatinine of 90 µmol/L (1.02 mg/dL) was measured in an icteric sample by a routine method, whereas a creatinine concentration of 125 µmol/L (1.41 mg/dL) was measured in the same sample by a reference method. For creatinine, the maximum allowable deviation amounts to 11.5 % (204). The result deviates by 35 µmol/L, which is 28 % from the expected value. Both criteria confirm that hyperbilirubinaemia is a clinically relevant interference when creatinine is measured using the routine method established in the laboratory.

5.2 General recommendations

Documentation of interferences
Documentation of method: Each clinical laboratory should specify the constituents in the quality manual that are affected by any of the following properties of the sample. The limits, beyond which the analysis shall not be performed, should be stated for each method that is subject to an interference. The European Directive for In Vitro-Diagnostics (IVD) states that providers of reagents must define the appropriate limiting conditions (62). The procedure for the detection of interfering properties as well as actions that should be taken with the sample, should be documented in the quality manual.

Detection of a potentially interfering property and handling of sample and request
Each sample must be visually examined immediately after arrival, or after centrifugation (in the case of blood samples) and the potentially interfering property recorded in the laboratory journal and report. When no visible interference is observed, it should be registered in the list by the notation: "appearance unremarkable".

The requests should be reviewed to identify analytes that could be affected by the observed interference in the sample. Analytes that are not affected by the interference in the sample are measured as in samples that contain no interference using the routine method of analysis. A sample that may be expectedly affected by an identified interference must be pre-treated to eliminate the interference before measurement is made; alternatively a measurement method may be used that is not subject to the interference. The analysis should not be made when a clinically relevant bias is expected, or if the interference cannot be eliminated or circumvented by an appropriate alternative method.

Reporting results
Each report should include a notation characterising the sample's "appearance". The observation should be documented for each sample: e.g. "haemolytic", "icteric", "opalescent", "turbid", or "lipaemic", if a relevant colour or turbidity was identified.

The report should indicate that the analysis was made despite a remarkable appearance of an interferent in the sample. The report should also indicate when the sample was pretreated prior to the analysis. If the interference in a sample cannot be eliminated for a subsequent analysis, the text "impaired by..." should replace the report of the result.

5.3 The haemolytic sample and the effect of therapeutic haemoglobin derivatives

Definition and mechanisms of haemolysis

Haemolysis is defined as the release of intracellular components of erythrocytes and other blood cells into the extracellular space of blood (92). Haemolysis can occur in vivo (e.g. through a transfusion reaction or during malaria parasite infection affecting the invaded erythrocytes), and in vitro during all steps of the preanalytical phase (sampling, sample transport and storage).

Haemolysis is caused by biochemical, immunological, physical and chemical mechanisms (23, 92). During blood transfusion, complement-dependent haemolysis may be caused by antibodies reacting with the major blood group antigens. Physical haemolysis is caused by destruction of erythrocytes by hypotonicity (e.g. dilution of blood with hypotonic solution), as well as decreased (vacuum) or increased pressure. Mechanical haemolysis may occur during the flow of blood through medical devices (e.g. catheters, heart valves) in vivo, during inadequate centrifugation as well as at elevated temperature in vitro. Contaminating substances may also cause invitro haemolysis. Finally, detergents (residual cleaning agents and disinfectants) and other contaminating substances may cause haemolysis.

After the separation of blood cells, haemolysis may be visible by the red colour of serum or plasma. The sample may concomitantly be contaminated by constituents of other blood cells (leukocytes and platelets). For example, cell breakdown may result in changes in blood of patients with leukaemia; the disintegration of platelets during coagulation results in higher concentrations of intracellular platelet constituents in serum (163). On the other hand, the intracellular components of erythrocytes are also released into plasma without a concomitant increase in haemoglobin concentration during storage of whole blood in refrigerators.

Haemoglobin based oxygen carriers used as blood substitutes

Therapeutic haemoglobin derivatives (so-called HbOC = haemoglobin-based oxygen carriers) were recently developed as blood substitutes. The substitutes occur at concentrations of up to 50 g/L in plasma of patients under blood substitute treatment. Plasma or serum containing blood substitutes has a strong red colour (32, 125, 283).

Detection and measurement of haemoglobin in serum or plasma

Visual detection

At extracellular haemoglobin concentrations above 300 mg/L (18.8 µmol/L), haemolysis is detectable by the red colour of serum or plasma. Samples with therapeutic haemoglobin derivatives (in therapeutically effective concentration) are always intensely red coloured.

Spectrophotometric detection

Some analytical systems measure the extent of haemolysis by comparing the absorption of samples at two wavelengths (88). The absorption spectrum of the haemoglobin derived oxygen carriers used as blood substitutes does not differ substantially from that of natural haemoglobin.

Analytical measurement

Haemoglobin in plasma or serum is measured at concentrations that are below the concentration visible to the human eye (16, 144, 255).

Distinction between in vivo haemolysis and in vitro haemolysis

Invivo haemolysis may be distinguished from invitro haemolysis by comparing a haemolytic sample of a patient with other samples from the same patient, arriving at the same time.

In vivo haemolysis

Free haemoglobin invivo rapidly binds to haptoglobin and the complex is eliminated from the circulating blood (as in haemolytic anaemia). Consequently, haptoglobin is reduced during intra-vasal haemolytic processes. The measurement of low concentration of haptoglobin thus permits an imperative assessment of haemolysis (exceptions are inborn haptoglobin deficiency and newborn children (268)). Likewise, the measurement of haemopexin and/or methaemoglobin/albumin was used to characterize invivo haemolysis (268).

A rise in concentration of indirect bilirubin and reticulocyte counts is a typical sign of in vivo haemolysis, which in turn leads to increased erythropoesis. Other consequences of in vivo haemolysis, such as a change in the LDH isoenzyme pattern, seem less suitable for the identification of haemolysis because of their low diagnostic sensitivity and specificity.

In vitro haemolysis

After in vitro haemolysis all constituents of erythrocytes, including potassium concentration, lactate dehydrogenase and aspartate aminotransferase activities, increase in addition to the concentration of free haemoglobin in plasma or serum (279). In contrast, haptoglobin concentration in plasma/serum of haemolytic samples remains unchanged. Certain immunological methods differ in their ability to distinguish haemoglobin/haptoglobin complexes from free haptoglobin (268).

Identification of haemoglobin derived oxygen carriers
Therapeutic haemoglobin derivatives yield a visible haemoglobin concentration within the range of 10 - 50 g/L. The absorption spectrum of haemoglobin derived oxygen carriers is not distinguishable from that of haemoglobin (32, 125, 283). However, haemoglobin concentrations of this magnitude rarely occur in vivo; therefore the use of therapeutic haemoglobin derivatives must be suspected at this plasma haemoglobin concentration. Haptoglobin cannot be used for discrimination, since the oxygen carriers only form complexes slowly with haptoglobin.

Mechanisms of interference by haemolysis
Haemolysis in vivo or in vitro can cause an apparent decrease or increase of results. A variety of mechanisms are contributing to these effects, some of which are summarized below:

Rise of intracellular constituents in the extracellular space
Cell constituents with an intracellular concentration 10 times higher than the extra-cellular concentration, will increase in plasma/serum during haemolysis (e.g. potassium, lactate dehydrogenase, aspartate aminotransferase). Differences of analyte concentrations between plasma and serum are also due to lysis of blood cells (essentially by platelets): thus, neuron specific enolase, potassium and acid phosphatase are higher in serum.

Interference with analytical procedure
Blood cell constituents can directly or indirectly interfere in the measurement of analytes. Adenylate kinase released from erythrocytes causes an increase of creatine kinase and CK-MB activity especially when inhibitors of adenylate kinase in the assay mixture are inadequate (248). In contrast, adenylate kinase does not affect the immunochemical quantification of CK-MB. Pseudo-peroxidase activity of free haemoglobin interferes in the bilirubin procedure of Jendrassik and Groof by inhibiting the diazonium colour formation (267). Proteases released from blood cells reduce the activity of coagulation factors while fibrin split product formation may increase.

Optical interference by haemoglobin
The effect of haemolysis on various analytes measured in clinical chemistry has been thoroughly investigated (25, 88, 238). Most often, the colour of haemoglobin increases the absorption at a respective wavelength or changes the blank value. An apparent increase or decrease of a result by haemoglobin is therefore method- and analyte concentration-dependent. Likewise, the changes caused by therapeutic haemoglobin derivatives are primarily due to optical interference (32, 125, 283).

Means to avoid haemolysis and its interferences
Haemolysis in vitro can almost always be avoided, when the mechanism of haemolysis is known. Therefore each haemolytic sample should be documented and the cause of haemolysis identified.

The most frequent causes of haemolysis, such as errors during sampling, are avoided using standardised materials and methods for the preanalytical processes and by training and individual counselling.

Occasionally reliable results can only be obtained from a truly non-haemolytic sample. In some cases, the interference can be reduced or excluded using a method that is not sensitive to haemolysis or by pre-treatment of the sample. Procedures including deproteinisation or molecular sieving (71, 73) and others, have been found to be not useful, because of the work load involved. Today, a modification of the methodology, e.g. by using a blanking procedure by means of measurement at a second, appropriate wavelength, is preferred, although, this procedure may not be applicable for the analysis of blood from patients who received blood substitutes (85). Likewise the ultrafiltration procedure, as applied in the multi-layer film technology, reduces the effect of interference by haemolysis (240).

Reaction upon the receipt of haemolytic samples
Each laboratory should document the procedures that are affected by haemolysis and to what extent they are affected. The procedures on how to handle haemolytic samples should be described in the quality manual. This includes the criteria for rejecting the execution of analysis.

The haemolysis of each sample must be documented and reported to the clinician who ordered the analysis.

When haemolysis occurs in all samples of a patient, haemolysis in vivo may be suspected. This must be immediately reported to the clinician to verify the possible causes of haemolysis or the possible use of synthetic haemoglobin derivatives.

After estimation of the degree of haemolysis the sample is treated for analysis according to the degree of interference. The results of measurement may be reported as follows:

- Method not impaired: report results as with non-haemolysed samples.
- Method impaired, but eliminated by pre-treatment: report results after pre-treatment.
- Method impaired in a clinically relevant way: instead of providing a result, report: "Impaired by haemolysis".

It is not recommended to correct a measured result for haemolysis arithmetically using the haemoglobin concentration as an indicator.

5.4 The lipaemic sample

Definition

Lipaemia is a turbidity of serum or plasma which is caused by elevated lipoprotein concentrations and which is visible by the eye. A sufficiently transparent sample container is a prerequisite to detect lipaemia. Visible detection of lipaemia is also dependent on the type of plasma lipoproteins at elevated concentrations in the sample. Post-centrifugal coagulation of serum samples of heparinised patients can also be the cause of turbidity.

Causes of lipaemia (turbidity)

Most often, lipaemia results from increased triglyceride concentration in plasma/serum. This can be due to food intake, altered lipid metabolism or infusion of lipids. After intestinal absorption, triglycerides are present in plasma as chylomicrons and their metabolites (remnants) for six to twelve hours.

One to four hours after intake of a "Continental" or "American" breakfast, plasma triglyceride concentrations increase substantially. As they cause turbidity of the sample, the patient should be requested to fast before investigations are made that are affected by lipaemia.

The following causes of plasma turbidity should also be distinguished: Metabolic disorders causing hypertriglyceridemia, lipid infusions, cold agglutinins and monoclonal immunoglobulins.

Identification and quantification of lipaemia

Visual and photometric methods for serum and plasma samples

In whole blood triglyceride concentrations above 1000 mg/dL (11.3 mmol/L) cause turbidity that is detected by visual inspection. Lipaemia in plasma or serum is visually observed at triglyceride concentrations above 300 mg/dL (> 3.4 mmol/L). The extent of turbidity of serum/plasma samples is measured at wavelengths above 600 nm (e.g. 660/700 nm) (240).

Detection in EDTA blood

Haematological tests are influenced by lipaemia. Thus, haemoglobin concentration is apparently increased by light scattering. The turbidity is detected by spectrophotometric analysis. The result of a centrifuged sample from the same patient taken at the same time can be used for comparison.

Mechanisms of the interference by lipaemia on analytical methods

Interferences in spectrophotometric analysis

Lipaemia interferes in photometric measurement by light scattering and light absorption. The apparent result can be either increased or reduced depending on the blanking procedure. At high turbidity, no measurement may be possible due to the limits of the linearity of the method (9).

Volume depletion effect

Lipoproteins decrease the apparent concentration of the analyte by reducing the available water of sample volume, since the volume occupied by lipoproteins in plasma or serum is included in the calculation of the analyte concentration. This explains why lower sodium and potassium concentrations are found in lipaemic sera, when plasma or serum is measured by flame photometry and by indirect measurement using ion-sensitive electrodes, in contrast to direct potentiometry (141). The same observation is made after centrifugation, when the lipoproteins are not homogeneously distributed in serum/plasma samples: the concentration of an analyte dissolved in the aqueous phase is less in the upper layer than in the lower phase of the sample. The converse is true for concentration of lipids and lipid soluble constituents, including certain drugs that are taken up by lipoproteins.

Interference by physico-chemical mechanisms

A constituent that is extracted by lipoproteins may not be accessible for the reagent, such as an antibody, for detection. Similarly, electrophoretic and chromatographic procedures may be affected by lipoproteins present in the matrix.

Means to avoid lipaemia and interferences caused by turbidity

To avoid interference of lipoproteins on measurement after oral intake of fat, the patient should fast at least twelve hours before blood samples are taken (100, 253). In patients receiving parenteral infusion of lipids a period of eight hours of interruption of the treatment is necessary to avoid interfering turbidity (99). If these measures do not provide a non-turbid sample, other causes of turbidity should be suspected.

Several methods were recommended to remove lipids from serum or plasma, such as centrifugation, to produce a clear infranatant sample. Other methods include the extraction of lipids with organic solvents or fluorine chlorinated hydrocarbons (e.g. Frigen®) and the precipitation of triglyceride rich lipoproteins by polyanion and cyclodextrin (227).

Centrifugation

Centrifugation at 1000 *g* is effective, when chylomicrons cause turbidity. In contrast, at least10 min centrifugation at 12 000 *g* separates serum or plasma lipids by flotation.

The clear infranatant must be carefully separated for analysis. Ultra-centrifugation must be employed for the separation of low density lipoproteins and high-density lipoproteins. A centrifugation time of at least 30 min at a speed above 40 000 *g* is recommended. The separation of lipaemic plasma from EDTA-blood in samples used in haematology can be performed by centrifugation and exchange of the cell-free supernatant with the same volume of isotonic NaCl solution.

Polyethylene glycol
The plasma/serum sample is mixed 1 + 1 (v/v) with 8 % polyethylene glycol 6000, incubated for 30 min in a refrigerator at 4 °C and centrifuged afterwards for 10 min at 4 °C and approx. 1000 *g*. The results determined in the clear supernatant are multiplied by the dilution factor 2 (199, 215).

α-*Cyclodextrin*
200 g α-cyclodextrin is dissolved in 1 L distilled water and kept in a refrigerator. Before use, α-cyclodextrin solution must be brought to ambient temperature. Thoroughly mix one part of α-cylodextrin solution with two parts of serum, and centrifuge for 1 min at 10 000 g. The clear supernatant can be used for analysis. The dilution must be considered when calculating the concentration of the constituent in the original serum sample.
Experiments revealed that the results on 20 serum constituents are not affected by the precipitation of lipoproteins using α-cyclodextrin (227).

Other methods for delipidation
Four different procedures for the extraction of lipids from serum samples were examined (3), including Freon 113®, dextrane sulfate 500 S, Aerosil 300 and a butanol/diisopropylether mixture. It was found that the delipidation methods may substantially alter the concentrations of certain analytes. Even the use of magnetic beads is not generally applicable (97).

Optical clearing systems
Commercial test kits may contain detergents such as triton X-100, cholic and desoxycholic acid, lipase or cholesterol esterase to remove turbidity in plasma or serum samples. The assigned concentrations of these substances are method dependent and should not be changed by the user.

Recommendation
A visible turbidity of a sample must be documented and reported with the results. Transparent sample containers must be used to detect turbidity. The methods used for the measurement of certain analytes that are affected by lipaemia must be listed; the methods for delipidation and the criteria for their application must be documented in the quality manual.

The method of choice for removal of turbidity from serum and plasma is a 10 min centrifugation in a micro-centrifuge with 10 000 *g*.

When chemicals are added (e.g. polyethylene glycol, α-cyclodextrin), the laboratory must prove that the assigned method for measurement is not disturbed by the agent.

Samples submitted for the determination of lipids and other analytes may be delipidated only after measurement of the lipids. This also applies to lipid-soluble drugs.

Test of interference by lipaemia
Various problems should be considered when examining the influence of lipaemia on analytical methods. Unfortunately, there is no uniform human lipid standard available. Patient samples with high lipid concentrations should not be frozen.

A 10 or 20 % emulsion of vegetable fat as applied in parenteral nutrition (5, 28, 41, 88 , 147, 177, 209) is suitable to simulate lipaemia . Significant differences between the effects of the "physiological" and the artificially produced lipaemia were observed, particularly in measurements of urea and potassium (41). Therefore because the observations may not be transferable to the biological condition the effect of lipaemia may not be examined using exclusively a model that contains artificial fat emulsions.

5.5 The icteric sample

Appearance of different bilirubin species

Bilirubin occurs in plasma as a free molecule and covalently bound to albumin. In addition, water-soluble bilirubin conjugates exist as mono- and diglucuronides (12). Studies on bilirubin interference were based mainly on experiments in which free bilirubin or water-soluble di-taurobilirubin was added to serum (39). Under certain conditions the bilirubin molecules differ qualitatively and quantitatively in their effects of interference (88).

Conjugated bilirubin appears in urine, when present at increased concentrations in blood. In patients with proteinuria, bilirubin bound to albumin can also appear in urine.

After intra-cerebral bleedings non-conjugated (free) bilirubin causes xanthochromia of the cerebrospinal fluid. At increased permeability of the blood-brain barrier bilirubin bound to albumin can appear in the CSF.

Mechanisms of bilirubin interference

Spectral interference

Bilirubin has a high absorbance between 340 nm and 500 nm wavelengths. Therefore, the range of the linearity of a spectrophotometric procedure, using these wavelengths for the measurement of an analyte, can be a limiting factor because of the high background absorbance caused by bilirubin (70, 209). In coagulation analysers using turbidimetric principle, a bilirubin concentration exceeding 25 µmol/L causes clinically relevant changes of the measured values of antithrombin III. Interference of bilirubin at higher concentrations will also be significant in certain coagulation tests (210).

The reduction of absorption as a result of oxidation of bilirubin in alkaline solution is the main cause for bilirubin interference in modifications of the Jaffé method without deproteinisation (70).
In a strongly acid solution the absorption of conjugated bilirubin shifts to the UV wavelengths. Therefore bilirubin interferes in the determination of phosphate using the phosphomolybdate method through its reducing effect (55, 88).

Chemical interference

Bilirubin interferes in oxidase/peroxidase based test systems. Proportionally to its concentration bilirubin reacts with H_2O_2 formed in the test system which causes systematically lower results in enzymatic procedures that are used for the measurement of glucose, cholesterol, triglycerides, urate and creatinine (88, 241). Bilirubin competitively interferes with dyes binding to albumin (153). However, di-taurobilirubin does not interfere in the procedure of dye binding to albumin (88).

Detection and documentation of increased bilirubin concentrations in clinical samples

The visual inspection of plasma or serum samples for the detection of hyperbilirubinaemia is often not sensitive enough. This is particularly true when samples are simultaneously stained by other pigments (e.g. haemoglobin and its derivatives). Moreover, adhesive labels on primary containers can impair visual inspection.

Hyperbilirubinaemia is directly detected in diluted samples that are measured at 450 and 575 nm (240). (The direct procedure of bilirubin measurement is only applied for the determination of hyperbilirubinaemia in newborns.) With the nutritional supply of carotines or carotinoids, bilirubin concentration by direct measurement is overestimated (77). The common clinical chemical methods are applied to quantitatively measure the interference caused by bilirubin. It is advisable to separate and measure the different bilirubin fractions to assess the mechanism of interference (12).

Prevention of bilirubin interference

Method selection

The high prevalence of hyperbilirubinaemia in patients from intensive care, gastroenterological, surgical or paediatric departments makes it pertinent to select analytical methods that are less susceptible towards bilirubin interference.

Blanking procedures are useful to eliminate spectral bilirubin interferences, (283). Parallel sample blank values give better results than methods in which reagents are added successively into a cuvette (88). Blanking procedures are often part of the analytical procedure, e.g. in the kinetic method for creatinine determination according to the Jaffé principle, when autoanalysers are used (220).

The chemical interference of bilirubin in an analytical reaction is not eliminated by blanking procedures. K_4 ($Fe(CN)_6$) effectively eliminates bilirubin interference in H_2O_2-forming enzymatic methods based on the Trinder reaction (8, 215,). Moreover, optimal concentrations of components of the Trinder reaction can reduce the interference by bilirubin. A mixture of non-ionic tensides may reduce bilirubin interference such as in the spectrophotometric determination of inorganic phosphate using phosphomolybdate (85).

Actions recommended for use in procedures sensitive to bilirubin

When procedures susceptible to bilirubin interference are used, the laboratory must know the limit of bilirubin concentrations where interference-free measurements are possible (application limit). The limit depends on the maintenance status of the analytical system and other variables. Unfortunately, manufacturers' data is not always available. For the determination of the application limit, 2 mL

of 20 mg free bilirubin, dissolved in 0.1 mol/L NaOH, is mixed with 20 mg ditaurobilirubin, dissolved in 2 mL distilled water, in the dark. Five mL of non-icteric pool serum is added to 0.1 mL of the master solution to prepare a final bilirubin concentration of approximately 340 µmol/L (20 mg/dL). Serial dilutions are prepared by mixing a non-icteric pool serum with the master solution at different proportions. The test solution must be used on the same day (39).

Suitable alternative procedures must be applied for samples that have bilirubin concentrations beyond the application limit. The procedures may require a pretreatment of samples to remove bilirubin. For the determination of serum creatinine using a bilirubin-susceptible enzymatic method the sample is pre-incubated with 4.4 kU/L bilirubin oxidase for 30 seconds (8). However, the low stability of bilirubin oxidase limits the practical application of this procedure. Ultrafiltration of serum was also used for the elimination of bilirubin interference in creatinine assays (73). As bilirubin binds to proteins, serum is centrifuged in a centrifugable ultrafilter (cut off ≈ 20 kD) for 15 min at 2000 *g* to remove bilirubin and obtain a completely protein-free ultrafiltrate. The volume depletion effect of proteins results in an approximately 4 % higher value for creatinine in the ultrafiltrate (73). The distribution of ionised low-molecular weight analytes on the diaphragm may be pH dependent which has an effect on the measurement results (71).

If procedures for the elimination of bilirubin are not applicable, alternative analytical principles should be applied. Immunological procedures for the measurement of serum albumin can be used to replace dye binding methods that are susceptible to bilirubin interference.

6. Table: Samples and Stability of Analytes

⊕ Recommended sample
\+ Can be used without changes of result
(+) Can be used with limitations (see comments, in case of citrated plasma this indicates the need to consider dilution by citrate (143).
– Not recommended
Descreased (↘) or increased (↗) results may be obtained in comparison to recommended samples.
Blank field means: no data was found in literature.
Greek letters refer to the information provided by diagnostic companies, numbers in brackets to the references.

6.1 Blood

Key for tables

Stability and half-life times
min = minute(s) h = hour(s)
d = day(s) w = weak(s)
m = month(s) y = years(s)

Information provided by Diagnostic Companies
α: Ortho-Clinical Diagnostics; Vitros Systems
β: Abbott; Axsym, Architect,
γ: Roche Diagnostics; Roche/Hitachi, Elecsys®, Modular
γγ: Roche Diagnostics; Cobas INTEGRA®
δ: Beckmann-Coulter; Synchron LX/CX, Immage/Array, Access
ε: Siemens Healthcare Diagnostics; Dimension®, BN-Systems, Stratus CS
Ω: Beckmann Coulter, Olympus-Analysers
κ: Siemens Healthcare Diagnostics; Immulite
λ: Bio-Rad
μ: Siemens Healthcare Diagnostics; ADVIA Centaur/ACS 180
σ: Siemens Healthcare Diagnostics, Enzygnost

Samples										Stability						
Analyte	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life		Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Acetaminophen															see Paracetamol	
Acetylsalicylate	+	+β	+β	(+)β				15-30 min								65
α_1-Acid glycoprotein (orosomucoid)	+	+γ,ε,Ω	+γ,ε,-γγ, Ω	(+)						11 d 4 w (2-8°C)	1 y	5 m	5 m			145, 258
Adenovirus antibodies	+		(+)												Complement fixation test, ELISA IgG, IgM	
Alanine aminotransferase (ALAT, ALT)	+	+	+	(+)				47 h		4 d↘	7 d	7 d	3 d↘			106, 140
Albumin colorimetric	+	+*	(+)↘+Ω	(+)				3 w		2-6 d 14 d (2-6°C)	4 m	5 m	2,5 m		*Bichromatic assay recommended for colorimetric assay(102).	27, 52, 76, 145, 222, 258, 271
nephelometric	+	+ ε	+ ε					3 w		6 d	3 m	1 w	4 h			
Aldosterone	+	+	⊕					min		1 d↘	4 d	4 d	4 d	EDTA		289
Alkaline phosphatase – total – bone isoenzyme	+↗ +	⊕ +	– –	(+) (+)↘				3-7 d 9-18 h		4 d↘ 4 d	2 m 1 m	7 d 7 d	7 d 7 d		EDTA binds essential cofactor zine.	100, 106, 271
Aluminium	–	–	–	–						7 d	1 y	2 w	1 w		Special tube needed	218
Amikacin	+	+	+β	(+)β				30 min-3 h			2 w	7 d	2 h			274, 290
Amiodarone	+	+	+					4 h-25 d		< 4 h	1 w	1 w	1 d		HPLC	100, 244
Amitriptyline	+	+	+					17-40 h					1 d		HPLC	275
Ammonia (NH_4^+)	–↗	(+)↗	⊕	–	+			min		15 min in EDTA↗	3 w	3 h	15 min	Serin 5 mmol/L + borate 2 mmol/L (72)	Do not use ammonium heparin. Contamination by sweat ammonia.	72
Amphetamines	+	+	+													275
Amylase – pancreatic – total	+ +	+ +	+ +	(+) (+)*				9-18 h 9-18 h		4 d↘ 4 d↘	1 y 1 y	1 m 1 m	7 d 7 d		*Possible decrease of the activity by Mg and Ca binding at > 25° C.	106, 161, 271, 289, 290
Amyloid A (SAA)	+	+ε									3 m ε	8 d ε	3 d ε			145

Table: Samples and Stability of Analytes

Samples

Stability

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Androstendione	+								1 d↘	1 y	4 d	1 d			132
Angiotensin converting enzyme (ACE)	+	+	–	–						1 y	7 d	1 d			164
Anticonvulsive drugs	+													See carbamazepine, ethosuccimide, phenobarbital, phenytoine, valproic acid	
Antimitochondrial antibodies (AMA)	+									1 m	7 d	1 d			43
Antineutrophil cytoplasmic antibodies (ANCA)	+									1 m	7 d	1 d			43
Antinuclear antibodies (ANA)	+									1 m	7 d	1 d			43
Antiphospholipid antibodies	+									1 m	2-3 d	1 d			43
Antistaphylolysine	+	+γ	+γ							6 m	2 d	2 d			
Antistreptodornase B	+									3 m	8 d				
Antistreptokinase	+														
Antistreptolysine	+	+β,γ,δ –γγ	+β,γ,δ, –γγ							6 m	8 d	2 d			
Antithrombin – functional – immunchemical	– –	–	– +δ, ε	⊕ (+)δ, ε			+*	40-135 h	8 h 2 d**	1 m 1 y	2 w 8 d	2 d		*Test by Pharmacia-Upjohn **after centrifugation	105, 137, 256, 259
α_1-Antitrypsin	+	+	+β, –γγ	(+)β, γ					11 d 7 w (2-6 °C)	3 m	5 m	3 m		EDTA and citrate↘	50, 145, 253, 254, 257, 289
APC resistance – functional screening test – genotyping factor V Leiden	– –	– –	–	⊕		⊕	⊕		30 min 1 w	6 m (–70°C)	3 h	3 h		Centrifuge within 30 min	292
Apolipoproteins AI, AII, B	+↗	+	⊕	(+)					36 h (4-8 °C)	3 m	8 d	1 d			44, 63 145, 189
Apolipoprotein CIII		+	⊕	(+)	(+)					1 m	1 m	1 m			145, 189
Apolipoprotein E	+		+						1 d	3 m	8 d				216
ApoE-genotyping						⊕			1 w (4-8 °C)	3 m	1 w			Stability of $ApoE_2$>$ApoE_4$>$ApoE_3$.	216, 229
Aspartate aminotransferase (ASAT, AST)	+↗	⊕	+, –α,Ω↘	(+)				12-14 h	7 d↘	3 m	7 d	4 d			106,140, 253 289,290
Aspergillus – antigen detection – antibody	+ +														
Atrial natriuretic peptide (ANP) – prohormone (pro ANP)			+* +					8,8 min 1 h	unstable 6 h	4 w	3 d	6 h	*Aprotinin	Centrifuge at 4 °C.	180, 184, 263

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
Barbiturates	+	+						50-120h
Bartonella spp. antibodies	+							
Batroxobin time	–	–	–	⊕				
Benzodiazepine	+	+						25-50 h
Bicarbonate	+	+	–		⊕			min
Bilirubin – conjugated – total (also in newborns)	 + +	 + +	 + +	 (+) (+)				 h 17 d
Biotin					⊕			
Blood cell surface markers (immunocytometry)					+	+		
Blood gases (CO_2, O_2, pH)					⊕			min
Bordetella pertussis antibodies	+	+δ	+δ	+δ				
Borrelia burgdorferi antibodies (Lyme disease)	+	+σ	+σ	+σ				
Brain natriuretic peptide (BNP) – NT-pro BNP	+ +	+μ +	⊕ +			⊕		13,4-20 min 2 h
Brucella antibodies (Brucellosis)	+							
C_1-esterase-inhibitor, functional assay, immunochemical	+ +		+	(+) ε + ε				
CA 125, (Cancer antigen125)	+	+α,γ,μ	+α,γ,μ	(+)γ				5-6 d
CA 15-3, (Cancer antigen15-3)	+	+α,γ,-μ	+α,β,γ,-μ	(+)γ				5-7 d
CA19-9, (Carbohydrate antigen 19-9)	+	+	+γ,μ	(+)γ				4-9 d
CA 72-4, (Cancer antigen 72-4)	+	+γ	+γ	(+)γ				3-7 d
Cadmium	–		⊕	–				10-35 y

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Barbiturates	2 d	6 m	6 m	6 m		See by phenobarbital	36, 65, 264
Bartonella spp. antibodies							
Batroxobin time		1 m	4 h	4 h		Avoid heparinate contamination ↗	105, 253, 289
Benzodiazepine	<1 d		5 m↘	5 m↘		See also diazepam, fluni-trazepam, nitrazepam	65, 135, 155, 264
Bicarbonate	unstable↘ (30 min - 2 h at 4° C)	1 m	7 d	1 d*	Keep tube closed	*1 h after opening the tube, see also blood gases	29, 140, 289
Bilirubin – conjugated – total (also in newborns)	unstable↘, ↗	6 m 6 m	7 d 7 d	2 d 1 d		Darkness required when stored >8 h.	27, 106, 271, 289
Biotin					deep frozen	uv-light sensitive	100
Blood cell surface markers (immunocytometry)	CD4 1 d in heparinised blood					See also lymphocyte subtypes	219
Blood gases (CO_2, O_2, pH)	<15 min↘ pO_2 <30 min, pH, pCO_2 <60 min on ice		2 h*		*In heparinised blood and closed tubes	Use closed gas tight tubes or capillaries	19, 29
Bordetella pertussis antibodies							
Borrelia burgdorferi antibodies (Lyme disease)						ELISA, Western blot	
Brain natriuretic peptide (BNP) – NT-pro BNP	4-5 h 1 d	5 d -8 m 1 y	1 d 5 d	4 h 3 d	EDTA		64,124,170, 175, 226, 233, 236
Brucella antibodies (Brucellosis)							
C_1-esterase-inhibitor, functional assay, immunochemical		1 m 1 y	2 d 8 d	6 h		Stabilise plasma by freezing.	253
CA 125, (Cancer antigen125)	2 d↘	3 m	5 d	3 d			22, 217, 246
CA 15-3, (Cancer antigen15-3)	7 d	3 m	7 d	7 d			151, 217, 237, 246
CA19-9, (Carbohydrate antigen 19-9)	7 d↘	3 m	30 d	7 d			217, 246
CA 72-4, (Cancer antigen 72-4)	3 d↘	3 m	30 d	7 d			217, 246
Cadmium	1 d in trace element tube					Special tube (Released from red stopper).	218, 289

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
Calcitonin	+	+	⊕					min-h
Calcium – total – ionised (free)	+ –	+ (+)	–↘ –↘	–↘ –↘	+ ⊕*			h min
Campylobacter jejuni/fetus antibodies	+							
Candida albicans – antibodies – antigen detection	+ +							
Carbamazepine	+	+α↗	+β,γ	(+)α↗, β,γ, Ω				10-25 h
Carbohydrate deficient transferrin (CDT)	+	+	+	(+)				5-10 d
Carcino-embryonic antigen (CEA)	+	+	+α↘,β,γ, μ	+γ				2-4 d
Cardiolipin antibody	+							
Catecholamines (epinephrine, norepinephrine)	–	⊕	(+)	–				3-5 min
Ceruloplasmin	+	+	+,–γγ					4 d
Chlamydia antibodies (C. trachomatis, C. pneumoniae)	+		(+)					
Chloramphenicol	+	+β	+	(+)				2-5 h
Chloride	+	+	–	–	+			1 h
Cholesterol	+	+	+,-α,γ,δ, Ω	(+)				
Cholesterol, HDL	+	+	+β,λ,γ,δ, –α	–				
Cholesterol, LDL	+	–,+β,γ,Ω	+β,–γ,Ω	–				
Cholinesterase, including dibucain number	+	+	+,–γ,Ω					10 d*
Ciclosporin	–	–	–	–		⊕		10-27 h
Circulating immuno-complexes (CIC)	+							
Clostridium tetani toxine antibodies	+							

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Calcitonin	4 h stabilised*	1 y	1 d	4 h	*Aprotinin 400 KIU/mL		100, 253
Calcium – total – ionised (free)	2 d↘ 15 min↗ 1 d *	8 m	3 w 2 h	7 d 3 d	*Use calcium-titrated heparin (24)	pH-dependent **Stable in gel tubes for 25 h & 72 h after centrifugation in closed tube (123).	108, 271, 289 24, 29, 123
Campylobacter jejuni/fetus antibodies							
Candida albicans – antibodies – antigen detection						Blood culture bottle	
Carbamazepine	2 d	1 m	7 d	5 d		10% higher results in plasma (α), unstable in gel separator tubes, but stable in SSTII tubes (30)	30, 36, 65
Carbohydrate deficient transferrin (CDT)	3 d	3 m	2 w	1 d		Method-dependent	224
Carcino-embryonic antigen (CEA)	7 d	6 m	7 d	2 d		EDTA reduces by 13% α	96,179,217, 237, 246, 269, 289
Cardiolipin antibody		1 m	2-3 d	1d			43
Catecholamines (epinephrine, norepinephrine)	1 h if not stabilised	1 m 6 m stabilised	 2 d	 1 d	Glutathione 1.2 g/L + EGTA (26)	EGTA plasma to be separated within 15 min and frozen at –20°C .	26, 99
Ceruloplasmin		1 y	2 w	8 d			254, 258, 271
Chlamydia antibodies (C. trachomatis, C. pneumoniae)			7 d	5 d		DNA-PCR possible after 3-4 d at room temperature.	173
Chloramphenicol							274
Chloride	1 d↘	y	4 w	7 d			29, 106
Cholesterol	2-7 d↗	3 m	7 d	7 d			11, 27, 44 63, 106
Cholesterol, HDL	2 d↗	3 m	7 d	2 d		3% lower cholesterol observed in EDTA plasma due to osmotic dilution effect	11, 44, 63
Cholesterol, LDL	1 d↘	3 m	7 d	1 d			11, 44, 63
Cholinesterase, including dibucain number	7 d↘	1 y	7 d	7 d		*Shorter in heavily diseased patients (76).	76, 106, 114, 246
Ciclosporin	13 d	3 m*	3 w*	3 w*	EDTA	*Stored in haemolysate	7, 66, 120, 274
Circulating immuno-complexes (CIC)	4 h	1 y	8 h	4 h			43
Clostridium tetani toxine antibodies							

Table: Samples and Stability of Analytes

Samples									Stability						
Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Coagulation factors															38, 105, 256, 292
Factor II	–	–	–	⊕				41-72 h	1 d	1 m		6 h			256, 292
Factor V	–	–	–	⊕				12-15 h	4 h	1 m	2 d	6 h		Centrifuge at 4°C.	38, 105, 256, 292
Factor VII	–	–	–	⊕				2-5 h	1 d	1 m	unstable	6 h			256, 292
Factor VIII	–	–	–	⊕				8-12 h		2 w	4 h	3 h			38, 105, 256, 292
Factor VIII R: Ag	–	–	–	⊕				6-12 h		6 m	7 d*	7 d*	*Sodium azide	Five freezing thawing cycles are possible.	261
Factor VIII R: Co				⊕				6 h		6 m	2 w*	2 d	*Sodium azide		261
Factor IX	–	–	–	⊕				18-30 h	1 d	1 m		6 h			256
Factor IX: Ag	–	–	–	⊕					1 d						292
Factor X	–	–	–	⊕				20-42 h	1 d	1 m		6 h			256, 292
Factor XI	–	–	–	⊕				3-4 d	1 d		unstable	6 h			256, 292
Factor XII	–	–	–	⊕				50-70 h	4 h		unstable	6 h			256
Factor XIII	–	–	–	⊕				8-10 d		1 m		4 h			256, 292
Cocaine Benzoylecgonin Ecgonine methyl ester	+	+	–						<10 min 5 d 10 d	4 d	30 d 5 d 10 d	<30 min 5 d 10 d	Fluoride, pH 5	Cocaine is converted in vitro into its metabolites	109, 155, 231
Cold agglutinins														Keep whole blood at 37° C (water bath).	
Complement C3	+	+	+,–γγ	(+)				min	1 d, 2 d ($C3_c$) (2-6 °C)	8 d	8 d	4 d		Dependent on antibody, during storage $C3_c$↗ C3↘	145, 258, 271, 289
Complement C4	+	+	+	(+)				12 h-1 d	1 d 2 d (2-6 °C)	3 m	8 d	2 d		During storage C4↘,$C4_c$↗	145, 271, 289
Copper	+	+	–	–					7 d	y	2 w	2 w		Special tube to avoid contamination.	271, 289
Corticotropin (ACTH)		+	⊕					min	1-4 h↘	6 w	3 h 1 d*	1 h 2 d*	Aprotinin 400-2000 KIU/mL Mercaptoethanol 2 µL/mL	Prevent binding to glass tubes by using plastic for storage. *EDTA plasma	64, 178, 201, 253
Corticotropin releasing hormone	+↘	+	⊕								2 d	11-18 h			64
Cortisol	+	+α,µ	+α,γ,µ					1 h	7 d	3 m	7 d	7 d		11% less in EDTA (α)	50, 126, 289
Corynebacterium diphtheriae toxine antibodies	+														
Coxiella burnetii antibodies (Q-Fever)	+														
Coxsackie virus antibodies	+														

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
C peptide	+	+	⊕					30 min
C-reactive protein (CRP)	+	(+)*	+α,γ,γγ, δ,ε,Ω	(+),+γ				2-4 h
		+α,γ,γγ, δ,ε,Ω						
Creatinine	+	+	+	(+)				3 min
Creatine kinase (CK)	+	+	+β,γ,δ, -Ω	(+)				18 h
Creatine kinase MB								
– enzyme activity	+	+,–α	+γ,δ,-Ω	(+)δ				12 h
– molecular mass	+	+β,γ,δ,-μ	+β,γ,δ,-μ	(+)γ				12 h
C-terminal crosslinks-CTX (β-Cross-Labs™)	+	+	⊕					
Cyclosporin								
Cyclic citrullinated peptide antibodies (CCP-antibodies)	+							
Cytokeratine fragment 21-1 (CYFRA 21-1)	+	+γ	+γ	(+)γ				2-5 h
Cystatin C	+	+	+					min
Cytokines		+	⊕					
– IFN-α, IFN-γ, -1α	–↘	+↗	⊕					
– IL-6	–↘	+	⊕					
– IL-1β, sIL-2R , sIL-6R	–↘		⊕					
Cytomegalovirus						⊕		
– antigen detection (pp65)						⊕		
– DNA ampflification								
– CMV antibodies	+	+β,σ	+β,σ	(+)β,σ				
D-Dimer	(+)	+	–	⊕				6-8 h
Dehydroepiandosteron sulfate (DHEA-S)	+	+β,γ	+β	(+)β				7-9 h
Dengue virus antibodies	+							
Diazepam	+	+	+					25-50 h
Differential leucocyte count	–	–	–	–		⊕	+	2 h-3 y
– Band neutrophiles								6-7 h
– Segmented neutrophiles								
– Eosinophiles								
– Basophiles								
– Monocytes								1,5-3 y
– Lymphocytes								
Digitoxin	+	+	+					6-8 d
Digoxin	+	+	+	(+)β				1-2 d
Disopyramide	+	+	+	(+)				4-9 h

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
C peptide	6 h	2 m	5 d	5 h	EDTA	Fluoride, oxalate also possible (β).	64, 79, 178
C-reactive protein (CRP)	3 w (2-6 °C)	3 y	2 m	11 d		*patient-dependent lower results	145, 258, 289
Creatinine	2 d↗	3 m	7 d	7 d			27, 106, 271, 289
Creatine kinase (CK)	7 d↘	1 m	1 m	4 h	Darkness	CK-BB not stable	106, 253, 271, 289
Creatine kinase MB					SH reagent		165
– enzyme activity	7 d↘	1 y	7 d	2 d			
– molecular mass	7 d↘	4 w	7 d	2 d			
C-terminal crosslinks-CTX (β-Cross-Labs™)	8 h 7 d (Crosslabs)	3 m	7 d	8 h 2 d*	pH 8.0, *EDTA	Stability pH-dependent.	157, 185
Cyclosporin						see ciclosporin	
Cyclic citrullinated peptide antibodies (CCP-antibodies)		1 y	7 d	1 d			43
Cytokeratine fragment 21-1 (CYFRA 21-1)	7 d	6 m	1 m	7 d			217, 246
Cystatin C		3 m	1 w	2 d		More stable in EDTA.	68, 145, 176
Cytokines	2 h (heparinised blood) 1 h (EDTA)		2 d 12 h↘			see also Tumor necrosis factor (TNF)	14, 48, 54, 59, 69, 145
Cytomegalovirus							
– antigen detection (pp65)							
– DNA ampflification							
– CMV antibodies							
D-Dimer	8-24 h 1 w	6 m	4 d	8 h			20, 31, 256, 292
Dehydroepiandosteron sulfate (DHEA-S)	2 d↘	y	2 w	1 d			51, 132, 253
Dengue virus antibodies							
Diazepam			5 m	5 m			65, 155, 264
Differential leucocyte count	2 h-7 d*				Dry blood smear stable	K_3- or K_2-EDTA: Stability temperature- and instrument-dependent. *Prepare blood smear within 3 h after sampling. Do not store EDTA blood refrigerator.	103, 107, 213, 242
– Band neutrophiles	2-12 h						
– Segmented neutrophiles	3-12 h						
– Eosinophiles	12 h-6 d						
– Basophiles	2 h-2 d						
– Monocytes	2-12 h						
– Lymphocytes	3 h-7 d						
Digitoxin		6 m	3 m	2 w			65, 289
Digoxin		6 m	3 m	2 w			65, 289
Disopyramide		5 m	2 w				65

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
DNA analysis by polymerase chain reaction amplification (PCR)	(+)	–*, +	+		–*	⊕	+	
Dopamine		+	+					3-5 min
Echinococcus spp. antibodies	+							
ECHO virus antibodies	+							
Elastase						+		
Electrophoresis, protein - see also Lipoprotein electrophoresis	⊕	(+)						
Endomysium antibodies	⊕							
Entamoeba histolytica antibodies	+							
Enterovirus antibodies	+							
Epstein barr virus – heterophilic antibodies (Paul Bunnel test) – anti-EBNA, -VCA, -EA	+ +	 +σ	(+) +σ	 +σ				
Erythrocyte count					(+)	⊕	(+)	2 m
Erythrocyte sedimentation rate (ESR)							⊕	
Erythropoietin	+	+	+					4-11 h
Estradiol (E_2)	+	(+)γ,μ, +α,β	(+)γ,μ, +α,β	(+)γ				
Estriol (E_3)	+	+						
Ethanol	+	⊕	+β,γ,γγ,δ	(+)β,δ		+*		2-6 h
Ethosuximide	+	+	+					30-60 h
Fatty acids	+	(+)↗*	(+)↘					2 min
Ferritin	+	+,–Ω	+β,ε,(+)*γ,–γγ,Ω	(+)γ,γγ				
α_1-Fetoprotein (AFP)	+	+	+	(+)				2-8 d
Fibrin(ogen) degradation products (FDP)	(+)*	–	–	(+)**				
Fibrin monomers	–	–	–	⊕				<1 h

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
DNA analysis by polymerase chain reaction amplification (PCR)	1 w					* Heparin inhibits Taq polymerase and restriction enzymes, LiCl 1,8 mol/L eliminates this error (122, 181).	37, 112, 122, 181, 270
Dopamine		1 m	2 d	1 d			253
Echinococcus spp. antibodies							
ECHO virus antibodies							
Elastase						see pancreatic elastase	
Electrophoresis, protein - see also Lipoprotein electrophoresis		3 w	3-7 d	1 d		Fibrinogen to be considered when using heparinate plasma, may be eliminated by fibrin precipitation.	253, 257
Endomysium antibodies		m-y	7 d	1 d			43
Entamoeba histolytica antibodies							
Enterovirus antibodies							
Epstein barr virus – heterophilic antibodies (Paul Bunnel test) – anti-EBNA, -VCA, -EA						IgG, IgM, IgA; ELISA, Western Blot	
Erythrocyte count	4 d 7 d (4-8 °C)						89, 107
Erythrocyte sedimentation rate (ESR)	2 h					1 part citrate, 4 parts blood	253
Erythropoietin	6-24 h	5 m		2 w		Shipped frozen.	129, 253
Estradiol (E_2)	1 d	1 y	3 d	1 d			51, 132, 289
Estriol (E_3)		1 y	2 d	1 d			
Ethanol	2 w↗↘**	6 m	6 m	2 w	EDTA/Heparin	*10 g/L NaF recommended to stabilise. **Evaporation, use closed tubes.	83, 155, 171
Ethosuximide		5 m	4 w				65
Fatty acids	30 min↗*	2 d	12 h	30 min		*Activitation of lipase by heparin. Freeze serum/ plasma immediately	271, 289
Ferritin	1 d	1-2 y	7 d	7 d		*Method-dependent	84, 252, 253, 289
α_1-Fetoprotein (AFP)	7 d	3 m	7 d	3 d			22, 128, 289
Fibrin(ogen) degradation products (FDP)	unstable↗↗	1 m	1 d	3 h	10 U thrombin and 150 KIU aprotinin/ mL blood	*Special tube **Aprotinin or soybean trypsin inhibitor.	178, 254, 256
Fibrin monomers	1 d	3 m	1 d	2 h			202, 256

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
Fibrinogen – immunochemical – Clauss	– –	+ –	– –	⊕ ⊕				4-5 d 4-5 d
Fibrinopeptide A	–	–	–	⊕				3 min
Flunitrazepam	+							
Folate – in erythrocytes	+	+,-μ	+β,-μ	(+)β	+μ	+β,δ		min
Follitropin (FSH)	+	+α,β,γ,μ	+α,β,γ,μ	(+)γ				min
Francisella tularensis-antibodies (tularemia)	+							
Free light chains (κ,λ) of immunoglobulins	+	+γ,δ,ε	+γ,δ,ε					2-6 h
Fructosamine	+	+	+					12 h
Galactose 1p-uridyltransferase (galactosemia sceening)						+*		
Gastrin	+	⊕*	+	(+)				
Gastrin releasing peptide (GRP), pro GRP	+	+	+					2 min 1 d
Gentamicin	+	+β,γ,γγ,δ	+β,γ,δ	(+)β				0,5-3 h (<30 y of age) 1,5-15 h (>30 y of age)
Glucagon	+	+	⊕					
Glucose – venous – capillary	–↘↘ –	–↘ –	–↘, +** –	–↘ –	(+)	⊕		min min
Glutamat decarboxylase autoantibodies (GADA)	+		+					
Glutamate dehydrogenase (GLDH)	+	+	+					18 h
Glutamate oxalocetate-transaminase (GOT)								
Glutamate pyruvate transaminase (GPT)								
γ-Glutamyltransferase (γ-GT)	+	+	(+)↘,+α,Ω	(+)↘,–γγ				3-4 d

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Fibrinogen – immunochemical – Clauss	1 w 1 w	1 m 1 m	7 d 1-7 d	7 d 1-7 d		Stability method-dependent	2, 15, 105, 183, 256, 259, 292
Fibrinopeptide A			2 h				256
Flunitrazepam	< 1 d*					*Store protected from light.	135
Folate – in erythrocytes	30 min↘, 5 d (2-8 °C)	8 w	1 d	30 min	Ascorbate 2g/L	Haemolysate, prepared by 0.5 mL blood + 4.5 mL ascorbic acid (2 g/L). Na-heparin interferes with Axsym-Test (β).	142, 253, 289, 290,
Follitropin (FSH)	7 d↘	1 y	2 w	2 w			127, 289
Francisella tularensis-antibodies (tularemia)							
Free light chains (κ,λ) of immunoglobulins		6 m	1 m	7 d			50, 145, 234, 250, 251
Fructosamine	12 h↗	2 m	2 w	3 d			249, 253
Galactose 1p-uridyltransferase (galactosemia sceening)						*In newborns drop of blood on filter paper, analysed in erythrocytes	
Gastrin	2 h			1 w*	*with aprotinin 2000 KIU/mL	Freeze serum as soon as possible.	64, 253, 289
Gastrin releasing peptide (GRP), pro GRP	1 h serum 3 h plasma	7 d	3-24 h	3-8 h*		*Plasma 8 h, serum 3 h.	246
Gentamicin	4 h	4 w	4 w	4 h			65, 290
Glucagon	Unstable		1,5 d	30 h	Aprotinin 500-2000 KIU/mL	Stabilise	178
Glucose – venous – capillary	10 min↘, 2 h** 10 min↘	1 d* 1 d*	7 d* 7 d*	2 d* 2 d*	Fluoride, mono-iodoacetate, mannose, acidity	*Stabilised haemolysate and plasma, **EDTA, citrate, fluoride tube (75).	57, 75, 81, 100, 253, 271, 289
Glutamat decarboxylase autoantibodies (GADA)						Add 25 mmol/L CaCl to EDTA plasma, centrifuge 10 min at 10000 *g*	182, 196
Glutamate dehydrogenase (GLDH)		4 w	7 d	7 d			253, 289
Glutamate oxalocetate-transaminase (GOT)						See aspartate aminotransferase	
Glutamate pyruvate transaminase (GPT)						See alanine aminotransferase	
γ-Glutamyltransferase (γ-GT)	1 d↘	y	7 d	7 d			106, 140, 253, 289, 290

Table: Samples and Stability of Analytes

Samples

Stability

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Glycated albumin														See fructosamine	
Gold	+														
Haematocrit					+	⊕			1 d 4 d (4-8 °C)		4 d*		*EDTA-blood	K_2- superior to K_3-EDTA	107
Haemoglobin A_{1c}						⊕		2 m	3 d (EDTA-blood)	6 m*	7 d*	3 d*		*Haemolysate	249
Haemoglobin F (HbF)						⊕		2 m							
Haemoglobin (whole blood)						⊕		2 m	4 d		7 d*	4 d *		*EDTA-blood	89, 107
Haemoglobin (plasma)	(+) ↘	⊕	⊕	(+)										Haemolysis during clotting (97).	16, 97, 144
Hantavirus antibodies RNA amplification	+				–	⊕	–								
Haptoglobin	+	+	+	(+)γ				3,5-4 d	8 d 7 w (2-6 °C)	3 m	8 m	3 m			254, 258, 271, 290
HbeAg	+	+β	+β	(+)β							7 d			also possible from ACD-B-, CRDA-1-, CPD- and Na-oxalate-tubes (β).	
HbsAg	+	+α,δ,σ	+α,δ,σ	(+)α,σ,↘δ				9 d		1 y	2 w	7 d			
Helicobacter pylori antibodies	+	+σ	+σ	(+)σ											
Heparin (anti Xa)				⊕								4 h			
Heparin associated thrombopenia; HEPA test	+						+		1 d		4 w			citrated blood and serum needed	
Hepatitis antibodies – anti-HAV – anti-HAV IgM – anti-HBs – anti-HBc – anti-HBe – anti-HCV – anti-Hepatitis D – anti-Hepatitis E	 + + + + + + + +	 +β,δ,σ +α,σ +α,β,σ +α,β,δ,σ +β,σ +α,β,δ +β	 +β,δ,σ +α,σ +β,σ +α,δ,σ +β,σ +α,β,δ +β	 (+)β,δ,σ +α,σ +α,β,σ (+)α,β,δ,σ (+)β,σ +α,–β,δ (+)β				9 d		 1 y 1 y 1 y 1 y 1 y 1 y	 4 w 4 w 4 w 4 w 4 w 4 w	 5 d 5 d 7 d 7 d 5 d 7 d		Prevent repeated freezing and thawing of sample.	100
Hepatitis B virus DNA	+		+								6 h				90
Hepatitis C virus – RNA amplification	+		+						6 h γ		3 d γ				111
Hepatitis D virus – RNA amplification	+		+												
Hepatitis E – RNA amplification	+		+												
Herpes simplex 1 or 2-virus antibodies	+	+σ	+σ	+σ											
HHV 6 antibodies (human herpes virus 6)	+														
HHV 6, 7, 8 – DNA amplification						⊕									

Table: Samples and Stability of Analytes

Samples									Stability						
Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
HI virus-1 – (provirus) DNA amplification – RNA amplification			 ⊕			⊕		 5-14 d	 7 d↘			7 d 1-2 d		Several freezing/thawing cycles possible.	111, 112, 113 156
HI virus-1- and -2 antibodies	+	+α,β,σ	+β,δ,σ	(+)α,β,δ,σ							4 w	5 d			
HIV, virus load	–↘	–	⊕	(+)	+	⊕	+	5-14 d	7 d						266
HLA-ABC typing					⊕									Ammonium heparinised blood	
HLA-B27					+	⊕			1 d				Citrate phosphate-dextrose (CPD)		
HLA DR typing						⊕									
Homocysteine	+↗	+	⊕	(+)		⊕λ			1 h↗ 6 h (2-6 °C)	4 y	4 w	4 d	Sodium fluoride 4g /L blood	Sample with EDTA/acidic citrate (0,5 mol/L). Store blood at -4°C (277). Haemolysed EDTA sample in detergent stable for 2 d (194). Serum>Plasma.	6, 192, 194, 200, 208, 243, 277, 287
HTLV I – antibodies (T-cell leukemia) – (provirus) DNA amplification – RNA amplification	+		 +			⊕									 111
Human choriongonadotropin (hCG) – total – free	 + +	 +	 +β,γ	 (+)α↗,γ				 1-3 d 0,5-1,5 d	 2 d 24 h (2-8 °C)	 1 y 4 w	 7 d 2 d	 2 d			96, 127
3-Hydroxybutyrate					⊕				4 h			2 d		Deproteinisation of whole blood	100
IgA	+	+	+					6 d	8 d 1 m (2-6 °C)	8 m	8 m	8 m		EDTA and citrate↘	50, 145, 258, 271, 289
IgD	⊕		–↘					5 d		6 m	7 d	7 d			
IgE antigenspecific IgE	⊕ +	+	+	(+)γ				2,5 d	7 d	6 m	7 d	7 d			145
IgG IgG subclasses	+ +	+ +	+	–				3 w	11 d 1 m (2-6 °C)	8 m	8 m	4 m			50, 145, 258, 271, 289
IgM	+	+	+γ,δ,ε,Ω –↘γγ					5 d	17 d 1 m (2-6 °C)	6 m	4 m	2 m			145, 258, 271, 289
Immunoglobulin (free) light chains (κ, λ)														See free light chains (κ, λ) of immunoglobulins	
Influenza virus ABC antibodies	+														
Insulin	(+) ↘	+	+					5 min-6 h	15 min	6 m	6 d	1 d			64,79,151, 253, 289

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
Iron (Fe)	+	+	–↘	–↘				3 h
Islet cell antibodies (1A-2A)	+		(+)*					
JC polyoma virus – antibodies (progressive multifocal leukoencephalopathy, PML) – DNA amplification (PML)	+					⊕		
Lactate	–↗	–↗	–↗	–	(+)			min
Lactate dehydrogenase (LDH)	(+) ↗	⊕	(+)	(+)				10-54 h LDH 5 < LDH 1,2
Lead	–	–	–	–	(+)	⊕	(+)	
Legionella antibodies	+							
Leishmania spp antibodies (visceral leishmaniosis)	+							
Leptin	+	+	+					
Leptospira spp antibodies (Leptospirosis)	+							
Leukocyte count					+	⊕	+	6-7 h
Lidocaine	+	+β,γγ	+β					1-3 h
Lipase	+	+↘α,Ω	+Ω,–↘	–				7-14 h
Lipoprotein (a)	+	+γ,ε	+γ	–γ				
Lipoprotein electrophoresis	⊕	+*	+*	–				
Listeria monocytogenes – antibodies – DNA amplification	+					⊕		
Lithium	+	+*,α	–,+α	–				8-24 h
Lupus anticoagulant	–	–	–	⊕				
Lutropin (LH)	+	+	+α,β,μ					
Lymphocytic chorio-meningitis virus (LCM) – antibodies – RNA amplification	+					⊕		

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Iron (Fe)	2 h↗	y	3 w	7 d			271, 279, 289
Islet cell antibodies (1A-2A)						*See also glutamate decarboxylase autoantibodies (GADA)	182, 196
JC polyoma virus – antibodies (progressive multifocal leukoencephalopathy, PML) – DNA amplification (PML)							
Lactate	<5 min, unstable↗↗	1 m*	3 d 2 w*	8 h 6 d*	Mannose/fluoride, monoiodoacetate, deproteinisation	Use glycolysis inhibitor tube, if not immediately deproteinised. *Deproteinised in whole blood.	10, 253, 271, 289
Lactate dehydrogenase (LDH)	1 h↗	6 w	4 d	7 d		LDH in serum dependent on platelet number.	106, 167, 271, 289
Lead				7 d		special tube	218
Legionella antibodies							
Leishmania spp antibodies (visceral leishmaniosis)							
Leptin		2 y	2 m	3-6 d		Five freeze/thawing cycles possible.	64, 272
Leptospira spp antibodies (Leptospirosis)							
Leukocyte count	7 d		1 d*			See also differential count, *EDTA-blood	60, 89, 107, 159, 191
Lidocaine			6 h			Separator gel↘	133
Lipase		1 y	3 w	7 d		EDTA binds calcium (activator), 15% less activated in heparin(α).	253, 254, 271
Lipoprotein (a)	1 d (4-8 °C)	3 m	2 w	2 d			158, 189, 190, 227, 230
Lipoprotein electrophoresis			2-5 d			Store at –20° C with 15% sucrose.	
Listeria monocytogenes – antibodies – DNA amplification							
Lithium	1 h↘	6 m	7 d	1 d		*Do not use Li-heparin.	274
Lupus anticoagulant		6 m		4 h		Centrifuge platelet free.	43
Lutropin (LH)	7 d	1 y	5 d	3 d			51, 64, 127, 289
Lymphocytic chorio-meningitis virus (LCM) – antibodies – RNA amplification							

Table: Samples and Stability of Analytes

Samples

Stability

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Lymphocte subtypes					+	(+)			1 d (7 d*)					*Special stabiliser recommended (Cyto-Chex)	211
α_2-Macroglobulin	+	+γ,ε													50
Magnesium (Mg) – ionized	+↗ –	+*** ⊕*	– –	–↘ –	⊕ ⊕*				1 d↗** 1 h	1 y 3 m	7 d 1 m	7 d 4 h	*Mg-balanced heparin (15-50 KIU/L) (21)	**Separate blood cells before analysis (223), do not use siliconised tubes. ***higher obtained in Terumo gel-tubes	21, 57, 106, 223, 276, 289
Malaria – trypanosoma gambiense – plasmodium antibodies – plasmodium spp.	 +					(+) ⊕								Microscopic examination of whole blood. Blood film of capillary blood.	
Measles virus – antibodies – RNA- amplification	+					 ⊕									
Mercury (Hg)					+	⊕								Special tube	275
Methadon	+	+													
Methotrexate	+							2-4 h		6 m	3 d			Light↘	65, 254
Mikrofilarias					+	+								Concentrated sample	
β_2-Mikroglobulin	+	+γ,ε,Ω	+γ,ε,Ω	(+)				40 min	1 d	6 m	1 w	3 d			50, 145, 254
Morbilli virus antibodies DNA amplification	+	+				 ⊕									
Morphine total*	+	+							21 d 6 m (4 °C)	6 m	6 m	3 m		Light↘ *after hydrolysis	232
Mumps virus antibodies	+	+σ	+σ	+σ											
Mycobacterium spp. DNA amplification						⊕									
Mycoplasma pneumoniae antibodies	+														
Myeloperoxidase (MPO)	+↗	+↗	+								7 d	8 h			228
Myoglobin	+	+	+	(+)γ				15 min	1 h↘	3 m	1 w	2 d			18, 49 145, 165 286
Neisseria gonorrhoeae antibodies	+														
Netilmycin	+							2-3 h							
Neuron specific enolase (NSE)	+↗	⊕	+					1 d	2 h↗	3 m 9 m (–80°C)	3 d	2 d	Heparin	Increased in thrombocytosis Serum>plasma.	35, 91, 197, 253
Nitrazepam	+	+β	+β	(+)β					1 d*	1 w	1 w			*Light↘	155, 265
Opiates	+	+							8 h	6 m	2 d	8 h		See also morphine	275
Osmolality	+	+								3 m	1 d	3 h			253, 289

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
Osteocalcin	+*	+*	⊕*					min
Pancreatic elastase	+		+	+				
Pancreatic polypeptide	+	+	+					
Paracetamol	+	+	+	(+)				1-4 h
Parathyrin (PTH)	+κ ↘	+γ,κ	⊕	(+)γ				3-4 min
Partial thromboplastin time (aPTT)	–	–	–	⊕				
Parvovirus B 19 – antibodies (erythema infectiosum) – DNA amplification	+					⊕		
Phencyclidine	+							
Phenobarbital	+	+	+	(+)β,γ,δ				2-6 d
Phenytoine free	+ +	+ –α –α,Ω +γγ	+β,γ,δ, –α,γγ,Ω	(+)β,γ +α				1-8 d
Phosphate, inorganic	(+) ↗	⊕	–α, γγ,Ω +μ	(+) μ, –α				min
Polio virus 1, 2, 3 – antibodies	+							
Potassium (K)	(+) ↗	⊕	–	–	+			min
Prealbumin								
Primidone	+	+	+	(+)				4-19 h
Procainamide and N-acetyl-procainamide (NAPA)	+	+β,γγ	+β,γ	(+)β				3-5 h 6-10 h
Procalcitonin	+	+δ	+	(+)				20-26 h
Procollagen type I and its N-terminal propeptide (PINP)	+	+	+					
Pro-gastrin releasing peptide (proGRP)								
Progesteron	+	+β,–α, μ↘	+β,μ,–α					

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Osteocalcin	15 min	8 w (-30 °C)* 1 y**	2 d, 4 d**	8 h, 2 h**	*Aprotinin 2500 KIU/mL + EDTA (5mmol/L)	Three freezing/thawing cycles are possible. **N-MID-osteocalcin in EDTA plasma	56, 146, 281
Pancreatic elastase		6 m	2 w				
Pancreatic polypeptide			6 d	2 d			64
Paracetamol	8 h	45 d	2 w	8 h			65, 274, 275, 290
Parathyrin (PTH)	6 h (2-3 d in EDTA-blood)	4 m	1 d	6 h	EDTA	15% lower concentrations in serum compared to EDTA plasma.	151, 212
Partial thromboplastin time (aPTT)	1 d	1 m	2-8 h	2-8 h		Stability reduced in plasma of heparinised patients	1, 2, 38, 105, 134, 256, 292
Parvovirus B 19 – antibodies (erythema infectiosum) – DNA amplification							
Phencyclidine							
Phenobarbital	2 d	6 m	10 d	1 d			36, 65
Phenytoine free	2 d	5 m	1 m	2 d		Unstable in serum separator tubes (36), but stabile in SSTII tubes (30). Biological half-life shorter in children.	30, 36, 65, 290
Phosphate, inorganic	1-16 h↗↗	1 y	7 d	3 d		Platelet-dependent in Serum (163).	27,106,163, 271, 289
Polio virus 1, 2, 3 – antibodies						Neutralisation test	
Potassium (K)	1-16 h↗↗	1 y	6 w	6 w		Platelet-dependent in serum >plasma (96, 163, 271), haemolysis↗.	27,57,99, 106, 163, 271, 289
Prealbumin						see Transthyretine	
Primidone	1 y	5 m	4 w				65
Procainamide and N-acetyl-procainamide (NAPA)		6 m	2 w				65, 254
Procalcitonin	1-2 d		4 d	4 h			168, 245
Procollagen type I and its N-terminal propeptide (PINP)		1 y	2 d	1 d			100
Pro-gastrin releasing peptide (proGRP)	7 d			7 d		see Gastrin releasing peptide	246
Progesteron	7 d	1 y	4 d	1 d			51, 289

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
Proinsulin	+↘	+	⊕					15 min
Prolactin	+	+β,δ,μ	+β,μ	–				
Propaphenone	+	+						
Propoxyphene	+	+						
Prostata specific antigen (PSA) – free – total	 + +	 +γ +γ,μ,–α	 +γ +γ,μ,–κ	 (+)γ				 2 h 2-3 d
Protein, total	+↘	⊕	+γ,γγ,δ,Ω	(+)				Complex
Protein C	–	–	–	⊕				6-8 h
Protein S	–	–	–	⊕				24-58 h
Protein S100	+							2-5 h
Prothrombin time (thromboplastin time, Quick)	–	–	–	⊕				
Pyruvate	–↘	–↘	–	–	+*			
Quinidine	+	+β, γγ	+β	(+)β				6-9 h
Renin	–	–	⊕	–				
Reovirus antibodies	+							
Respiratory syncytial virus (RSV) antibodies	+							
Reticulocyte count maturity index					(+)	⊕ ⊕		12 h
Retinol binding protein (RBP)	+	+						10 h
Rheumatoid factors subfractions IgA, IgG	+ +	(+)γ,+Ω	(+)γ,+Ω	(+)γ				
Rickettsia antibodies	+							
RNA analysis by amplification (PCR)	(+)	–*	+		–*	⊕	+	
Rotavirus antibodies	+							
Rubella virus – antibodies – RNA amplification	+	+β,σ	+β,σ	(+)β,σ		 ⊕		

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Proinsulin	2 d*	6 m	1 h	7 min	EDTA	*in EDTA	79, 100, 193
Prolactin	2 d	1 y	6 d	5 d			51, 64, 289
Propaphenone							
Propoxyphene							
Prostata specific antigen (PSA) – free – total	 2 h-7 d 4-7 d	 1 m↗ 3 m- 2 y	 1 d 30 d	 6 h 7 d		Three freezing thawing cycles possible.	34, 121, 152, 187, 188, 203, 217, 225, 285
Protein, total	1 d	1 y	4 w	6 d		Plasma results higher due to fibrinogen (Biuret method).	253, 289
Protein C	1 w	3 m	7 d	7 d		Avoid freezing/thawing cycles.	105, 162, 292
Protein S	4 h	1 m	4 h	8 h		Separate cell-free plasma directly after centrifugation.	20, 105
Protein S100			7 d	7 d			246
Prothrombin time (thromboplastin time, Quick)	4 h-1 w*	1 m	8 h- 1 d*	4 h- 1 d*		*Reagent-dependent	1, 2, 105, 198, 253, 256, 292
Pyruvate	< 1 min*					*Only stable in deproteinised blood	
Quinidine		1-2 w	1 d				65, 274
Renin	Unstable	1 y		1 h			254
Reovirus antibodies							
Respiratory syncytial virus (RSV) antibodies							
Reticulocyte count maturity index	3 d* 1 d*		1 d* 1 d*			*EDTA blood	33, 159, 206
Retinol binding protein (RBP)		3 m	1 w	4 h			50, 145, 222
Rheumatoid factors subfractions IgA, IgG	6 h	3 m	8 d	1 d			151, 289, 290
Rickettsia antibodies							
RNA analysis by amplification (PCR)	2 h, 12 h (4°C) 4 d (EDTA) 1 m**	1 y	1 d	< 1 h	5 mmol/L Guanidinium-isothiocyanate **PAXgene™	*Heparin inhibits Taq polymerase and restriction enzymes LiCl 1.8 mol/L eliminates this error (122, 181)	111, 122, 195, 263
Rotavirus antibodies							
Rubella virus – antibodies – RNA amplification							

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life
S100 protein	+							2-5 h
Salicylate	+	+	+	(+)				24*-30 min
Sandfly (pappataci-) fever antibodies	+							
Selenium (Se)	–	–	–	–		+*		
Sirolimus						⊕		
Sodium (Na)	+	+	–	–	+*			min
Soluble transferrin receptor (sTfR)	+	+γ,γγ,ε	–ε					
Somatotropin (STH), (growth hormone)	+	+	⊕					20-50 min
Squamous cell carcinoma antigen (SCCA)	+	+						1,5-3 h
Staphylococcal antibodies – antitaphylolysin O	+	+γ	+γ					
Streptococcal antibodies – anti DNAse B – antihyaluronidase – antistreptolysin O – antistreptokinase	+ + + + +	+ +β,γ,δ +β,γ,δ	+ +β,γ,δ +β,γ,δ					
Tacrolimus	–	–	–	–	–	⊕		6-21 h
Tartratresistant acid phosphatase (TRACP 5b)	+	+	+					
Testosterone	+	+	+	(+)γ				
Tetrahydrocannabinol carbonic acid (THC)	+	+						~45 h
Theophylline	+	+	+	(+)α,β				3-12 h
Thrombin time	–	–	–	⊕				
Thrombocyte antibodies	+		+	+				
Thrombocyte count Thrombocyte volume					(+)↘	⊕ ⊕	(+)	9-10 d
Thrombocyte function using platelet function analyzer (PFA) (ε) using flow cytometry	– –	– –	– –	–			⊕ ⊕	9-10 d

Stability

Analytes	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
S100 protein			7 d	7 d		see Protein S100	246
Salicylate		6 m	2 w	7 d		*Higher at toxic concentrations	65, 274
Sandfly (pappataci-) fever antibodies							
Selenium (Se)	2 d	1 y	2 w	1 w		*Special tubes, contamination	218
Sirolimus	1 d* (4-8° C)	30 d	7 d	8 h	*EDTA-blood	LC-MS/MS	221
Sodium (Na)	4 d↘	1 y	2 w	2 w		*Use 140 mol/L Na-stabilized heparin 8-12 IU/mL blood (29).	57, 106, 289
Soluble transferrin receptor (sTfR)	2-6 h	3 m	7 d	3 d		Freeze only once	48, 145, 151, 253, 290
Somatotropin (STH), (growth hormone)	1 d	3 m	8 d	3 d	EDTA		51, 64, 289
Squamous cell carcinoma antigen (SCCA)	7 d	1 m	1 m	7 d	Closed tubes	*Increase by contamination (skin)	179, 217, 248
Staphylococcal antibodies – antitaphylolysin O							
Streptococcal antibodies – anti DNAse B – antihyaluronidase – antistreptolysin O – antistreptokinase	1 h	>1 m	3 d				100
Tacrolimus	7 d	1 y	2 w	7 d		LC-MS/MS	7, 100, 274
Tartratresistant acid phosphatase (TRACP 5b)	2 h	2 m		4 h			100
Testosterone	7 d 1 d in women↗	1 y	7 d	1 d			51, 132, 271
Tetrahydrocannabinol carbonic acid (THC)		6 m	6 m	2 m	Na azide	Unstable in plastic tubes.	65, 155
Theophylline		3 m	7 d	8 h			65, 264, 274
Thrombin time	1-4 h↗	1 m	1 h- 2 d*	1- 4 h*		*Stabiltiy reagent- and heparin-dependent.	38, 105, 256, 259
Thrombocyte antibodies							
Thrombocyte count Thrombocyte volume	4 d*, 7 d (4-8 °C)*				*in EDTA blood	Aminoglycosides avoid pseudothrombocytopenia in EDTA (214).	105, 107, 160, 214
Thrombocyte function using platelet function analyzer (PFA) (ε) using flow cytometry	4 h 2 h (7 d*)			1 h		*Special stabiliser recommended (211).	211, 219

Table: Samples and Stability of Analytes

Samples

Stability

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood Hep	Whole blood EDTA	Whole blood Citrat	Biological half-life	Stability in blood at room temperature	Stability in serum/plasma –20 °C	Stability in serum/plasma 4-8 °C	Stability in serum/plasma 20-25 °C	Stabiliser	Remarks/ Comments	References
Thyreoglobulin	+							1 d	2 d	1 m	3 d – 3 w	1 d		Three freezing/thawing cycles possible (45).	45, 253, 289
Thyreotropine (TSH)	+	+β,γ,μ, –α	+α,β,γ,-μ	(+)γ				min	7 d	3 m	3 d	1 d		Spot blood on filter paper in newborns.	51, 271, 289
Thyreotropine receptor-antibodies (TRAb)	+														
Thyroid antibodies Thyroid peroxidase antibodies (TPO), Thyroglobulin antibodies(anti-Tg^{Ab})	+	+									2 d				100
Thyroxine (T_4)	⊕	+β,γ,γγ, –α,μ	+β,γ,γγ, –α,μ	(+)γ				6 m	7 d	1 m	7 d	5 d			51, 271, 289
Thyroxine, free (fT_4)	+	+	+	(+)γ					6 h	3 m	8 d	2 d			151, 289
Thyroxine binding globulin (TBG)	+	+							7 d	1 m	5 d	5 d			57, 254, 289
Tick borne encephalitis virus antibodies	+		(+)												
Tobramycin	+	+β,γ,δ	+δ	(+)β				0,5-3 h (<30 y of age) 1,5-15 h (>30 y of age)		1 m	3 d	<2 h		Lower results obtained in heparinised plasma.	65, 207, 274
Toxoplasma gondii antibodies (IgA, IgG, IgM)	+	+β,σ	+β,σ	+β,σ							8 d	8 d			
Transferrin	+	+	+					7-10 d	11 d 3 w (2-6 °C)	6 m - 2 y	8 m	4 m			84,145,258, 271, 289
Transthyretine (prealbumin)	+	+γ,ε	+γ					≈2 d		1 y	6 m	3 d			222
Treponema pallidum antibodies – DNA amplification	+	+σ	+σ	+σ		⊕									
Tricyclic antidepressants	+	+β	+β	(+)β					1 w	1 y				see also Amitriptiyine	47, 275
Triglycerides	+	+	+,–α	(+)				3 h-3 d	7 d↗*	y	7 d	2 d		*Decrease of triglycerides, increase of free glycerol, but only minor increase of total glycerol.	44, 106, 271, 289
Trijodothyronine (T_3)	⊕	(+)↗ β,γ,δ,μ	+μ					19 h		3 m	8 d	2 d		Serum-plasma difference method dependent	271, 289
Triiodothyronine, free (fT3)	+	+	+	(+)γ						3 m	2 w	2 d			82,271,289
Troponin I	+	+β,δ,–↘α, μ	+δ,–↘α,μ			+		2-4 h		4 w	3 d	2 d			17, 80, 104, 165, 189, 247
Troponin T	+	+γ	+γ					2-4 h	8 h	3 m	7 d	1 d			80, 165, 247, 253
Tumor necrosis factor (TNF)	–		⊕						1 h				EDTA		54, 69
Urea	+	+	+					min	1 d↗	1 y	7 d	7 d		Do not use NH_4-heparin.	106, 289, 290, 291
Uric acid	+	+	+↘	(+)				min	3-7d↗	6 m	7 d	3 d			27, 271, 289, 290

Table: Samples and Stability of Analytes

Samples

Analytes	Serum	Heparinate Plasma	EDTA Plasma	Citrated Plasma	Whole blood			Biological half-life
					Hep	EDTA	Citrat	
Valprocic acid	+	+	+	(+)β				8-15 h
Vancomycin	+	+	+	(+)β				4-10 h
Varicella Zoster virus – antibodies – DNA amplification	+	+σ	+σ	+σ		⊕		
Vasoactive intestinale polypeptide (VIP)	↘	↘	⊕					
Vasopressin (ADH)	↘	+	⊕					
Vitamin A (retinol)	+		⊕					11 h
Vitamin B_1 (thiamin)	+	+	+			⊕		
Vitamin B_2 (riboflavin)		+	+			⊕		
Vitamin B_6 (pyridoxal phosphate)	(+)		⊕			⊕		
Vitamin B_{12} (cobalamin)	+	+	⊕					
Vitamin C (ascorbic acid)	+	+	+					
Vitamin D 1.25-dihydroxy-vitamin D (calcitriol), 25-hydroxy-vitamin D (calcidiol)	+ +	+ +	+ +					
Vitamin E (tocopherol)	+		⊕					
Vitamin K (transphyllochinone)			+					
von Willebrand factor			⊕					
Yersinia enterocolitica antibodies	+							
Zinc (Zn)	–	+	–	–				

Stability

Stability in blood at room temperature	Stability in serum/plasma			Stabiliser	Remarks/ Comments	References
	–20 °C	4-8 °C	20-25 °C			
2 d	3 m	7 d	2 d			36, 65
	7 d	1 d	2 d			65, 269, 274, 290
	>6 d	6 d	1 d	EDTA + aprotinin		64, 178
		6 d	1 d	EDTA	Freeze plasma	64
1 h	2 y	1 m	8 h		light sensitive	100, 253
5 h*	1 y	1 d*	5 h*		light sensitive, *in EDTA blood	100, 116
1 h	1 m	1 d*	5 h*		light sensitive, *in EDTA blood	100
1 d*	30 d*	3 d*	1 d*	EDTA, darkness	light sensitive, *in EDTA blood, Plasma, Serum	100, 116
6 h	8 w	1d	15 min	EDTA, darkness		100, 142, 151
3 h (4 °C)	3 w*	3 h		60 g/L metaphosphate, deproteinised	*Only with stabiliser	100
3 d 3 d	1 y 1 y	7 d 7 d	3 d 3 d		*Calcidiol light sensitive	100, 253, 275a, 289
8 h↘	1 y	1 m	8 h	EDTA		100, 253
unstable	3 m	unstable			UV light↘	100, 253
1 w						292
30 min↗	1 y	2 w	1 w		Special tube, avoid contamination by stopper.	218, 271, 289

6.2 Urine

Analyte	Stability in urine at –20 °C	4–8 °C	20–25 °C		Stabiliser	Comments	Reference
Albumin	6 m	1 m	7 d				110, 148, 250, 251
Aluminium	1 y	7 d	3 d				218
5 (δ)-Aminolevulinic acid	1 m	4 d	1 d		pH 6-7, stabilised with 0,3% $NaHCO_3$	Drugs↗ Light↘.	253, 289
Amphetamine	1y						53
Amylase	> 3 w	> 10 d	2 d			Saliva contaminates↗↗.	161
Bence Jones protein (immunoglobulin light chains κ, λ)	6 m	1 m	7 d				250, 251
Calcium	> 3 w	4 d	2 d		Acidify, pH < 2	Crystallisation at cool temperature	42
Catecholamines Norepinephrine Epinephrine Dopamine	Unstabilised 20 d Stabilised 1 y	4 d 1 y	4 d 3 w		Acidify pH < 2,5-5 (9 mL 20% HCl in 24 h urine) or EDTA (250 mg/L) and sodium metabisulfite (250 mg/L)		26, 172, 278
Citrate	4 w*		1 d*		*pH <1,7	*Unstable in native urine	108
Cocaine metabolite Benzoylecgonine	4 m	3 w			pH 5, ascorbic acid		53, 109, 155
Codeine	1 y						53
Copper	1 y	7 d	3 d				218
Cortisol, free	1 w	1 w	2 d		10 g/L boric acid		42, 126, 276
C-peptide		6 d	19 h				64
Creatinine	6 m	6 d	2 d				42, 253
Cystine (Cysteine)	> 1 y*	3 m*	7 d*		*Stabilized in HCl		108
Ethanol		30 d					83, 155
Glucose	2 d	2 h↘	2 h↘		10 mmol/L Azid	Bacteria decrease stability	42, 253, 254
5-Hydroxyindoleacetic acid	2 d	2 d	2 h		Acidify		253, 289
Hydroxyproline	5 d	5 d	5 d				253
Immunoglobulin G (IgG)	Unstable	1 m	7 d				110, 148, 250, 251
Iron	>1 y	7 d	3 d				42
Lysergic acid diethylamide(LSD)	2 m	1 m	1 m		HCl 1 Vol%		53, 155
α_2-Macroglobulin		7 d	7 d				
Magnesium	1 y	3 d	3 d		Acidify pH < 2		42, 108
Metanephrines			8 d				278
α_1-Microglobulin	6 m	1 m	7 d				110, 148, 250, 251
Morphine	1 y						53, 65, 155
Myoglobin	>12 d*	12 d*	12 d*		*pH >8.0	Unstable at acid pH	286
N-Acetyl-β, D-glucosaminidase (β-NAG)	1 m	7 d	1 d				166
Neutrophil gelatinase associated lipocalin (NGAL)		7 d	1 d				
N-telopeptides (NT_X)	4 w	5 d					
Osmolality	> 3 m	7 d	3 h				42
Oxalate	4 m (at pH 1.5)	unstable↘	<1 h		pH <2, HCl 1Vol %, thymol 5mL/L	Vitamin C↗	108
pH		unstable↗	unstable↗			Increase by NH_4 formation	42
Phosphate, inorganic		6 m < pH 5	2 d at pH <5.0		1 vol % thymol, 5 mL/L, pH <5	precipitates at alkaline pH	42, 108

Urine/Cerebrospinal Fluid (CSF)

Analyte	Stability in urine at –20 °C	4–8 °C	20–25 °C		Stabiliser	Comments	Reference
Porphobilinogen	1 m*	7 d*	4 d*		*pH 6-7 by $NaHCO_3$	Acid pH↘, Light↘	253, 289
Porphyrines Total porphyrine, Uroporphyrine, Heptacarboxyporphyrine, Hexacarboxyporphyrine Pentacarboxyporphyrine, Coproporphyrine Tricarboxyporphyrine, Dicarboxyporphyrine	1 m*	7 d*	4 d*		*0,3% $NaHCO_3$, pH 6-7	Light↘	100, 253
Potassium	1 y	2 m	45 d				42
Protein	1 m	7 d	1 d				42
Pyridinolines	> 1 y	1 w	3 d			UV-Light↘↘	100, 273, 281
Sediment of urine Acanthocytes Bacteria Epithelial cells Erythrocytes Leukocytes Casts (hyaline and others)		1-8 h 2 d 24 h↗ 1-4 h 1-4 h	1-2 h 1 d* 1-2 h↗*** 3 h 1 h, 24 h* 24 h** < 1 h↘*** 2 d		Osmolality >300 mosmol/kg	*>300 mosmol/kg **pH <6,5 ***pH >7,5 Do not freeze	42, 136, 138
Sodium	1 y	45 d	45 d				42
Test-strip fields Erythrocytes Leukocytes Nitrite Protein		1-3 h 1 d* 8 h	4-8 h 1 d↗ 4 h 2 h**			*>300 mosmol/kg **Unstable at pH 7,5	42, 136, 138
Transferrin	4 w	1 w	7 d				148
Urea	4 w	7 d	2 d		pH < 7		42
Uric acid	unstable		4 d		pH >8	Precipitation at pH <7	42, 108
Vanilliyl mandelic acid (VMA)	>1 y	>7 d	7 d at pH 3-5		pH <5		42, 253, 289

6.3 Cerebrospinal Fluid (CSF)

Analyte	Stability in urine at –20 °C	4–8 °C	20–25 °C		Stabiliser	Comments	Reference
Albumin	>1 y	2 m	1 d		Up to 1 h: Do not cool Up to 3 h: Transport on ice No additives No partial fixation Long term storage: Immediately –70 °C in glass or polypropylene vessels tightly closed.	Glucose, lactate: Stability depends on cell content. IgG: Freezing is not recommended. Leukocytes: Store cells as dry smears.	130, 131
Glucose	>1 m	3 d	5 h↘				
IgA , IgG, IgM	unstable	7 d	1 d				
Lactate	m	1 h	30 min↗				
Leukocytes		3-5 h	1-2 h				
Myeline basic protein (MBP)		2 w	2 d				61
Neuron specific enolase (NSE)	1 m, 6 m (-80°C)						197
Protein, total	> 1 y	6 d	1 d				130, 131
Tumor cells		1-12 h				Store cells as dry smears.	

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