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**USE OF ANTICOAGULANTS IN DIAGNOSTIC
LABORATORY INVESTIGATIONS**

1999

List of authors:

W:G.Guder, W. Ehret, F. da Fonseca-Wollheim, W. Heil, O. Müller-Plathe, G. Töpfer,
H. Wisser and B. Zawta.

List of contributors:

G. Banfi, Milan, A. Deom, Geneva, C.G. Fraser, Dundee, P. Hagemann, Zürich, J. Henny, Nancy,
A. Kallner, Stockholm, E.A. Leppänen, Helsinki, S.M. Lewis, London,
S. Narayanan, New York, M. Neumaier, Hamburg, M.A. Peça Amaral Gomes, Lisbon,
R. Probst, München, Y. Schmitt, Darmstadt.

R. Zinck, Wiesbaden Delkenheim, P. Mikulcik, München, R. Hinzmann, München,
A. Karallus, Heidelberg, M. Lammers, Marburg, M. Buchberger, Kremsmünster,
J. Kukuk, Limburg, H. Gross, Hanau, D. Klahr, Tuttlingen, D. Kolpe, Nümbrecht-Elsenroth,
S. Kreitlow, Liederbach, H. Kitta, Usingen, G. Gunzer, Clare, O. Sonntag, Neckargemünd,
S. Speidel, Mannheim, W. Brand, Nümbrecht, V.-J. Friemert, Deisenhofen, T. Kunert-Latus,
Frankfurt/Main, G. Hoffmann, Grafrath.

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1. INTRODUCTION

It is imperative that the in vivo state of the quantity in the body fluid under investigation be preserved unchanged for biochemical analysis to justify a medically valid conclusion. This is not always possible when measuring extra-cellular and cellular components of blood. Platelets and coagulation factors are activated when the blood vessels are punctured, and these processes continue when sample containers are used without an anticoagulant. Coagulation-related changes of some quantities can be largely avoided by using anticoagulants added to the sample containers. The types and concentrations of anticoagulants were defined for the preservation of venous blood samples and are now used for standardized collection of plasma around the world (1).

This recommendation compiles the findings described in the literature and those provided by the contributors to this document on the use of anticoagulants. The overview was developed during several meetings and after discussions with experts from the diagnostics industry.

2. DEFINITIONS

2.1 Whole blood

A venous, arterial or capillary blood sample in which the concentration and characteristics of cellular and extra-cellular quantities remain relatively unchanged when compared with the in vivo state.

2.2 Serum

The undiluted, extra-cellular portion of blood after adequate coagulation is complete.

2.3 Plasma

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

2.4 Anticoagulants

Anticoagulants are additives that inhibit blood and/or plasma to clot thereby ensuring that the quantity to be measured is changed as little as possible before the analytical process. Anticoagulation is achieved by either the binding of calcium ions (EDTA, citrate) or by the inhibition of thrombin activity (heparinates, hirudin). It is important that the blood be mixed with the following concentrations of solid or liquid anticoagulant immediately after sample collection:

The colour codes of tubes containing anticoagulants according to ISO 6710 are:

EDTA =	lavender;
citrate 9:1 =	light blue;
citrate 4:1 =	black;
heparinate =	green;
no additives (for serum) =	red (1).

2.4.1 A salt of ethylenediaminetetraacetic acid (EDTA)

Dipotassium (K_2), tripotassium (K_3) (1) and disodium (Na_2) are used as cations (2). Concentrations: 1.2 to 2.0 mg/mL blood (4.1 to 6.8 mmol/L blood) based on anhydrous EDTA. The International Council for Standardisation in Haematology (ICSH) recommended dipotassium EDTA as the choice because the tripotassium salt causes more artefactual changes in red cell size, increasingly more than three hours after blood collection (3).

2.4.2 Citrate

Trisodium citrate with 0.100 to 0.136 mol/L citric acid. Buffered citrate with pH 5.5 to 5.6: 84mmol/L trisodium citrate with 21 mmol/L citric acid. 0.109 mol/L (3.2%) was recommended (4-6). WHO and NCCLS recommend

3.2% since differences have been noticed between 3.2% and 3.8% when reporting INR using respective reagents (7,8). The International Society for Thrombosis and Hemostasis (ISTH) recommends the use of Hepes buffer for all investigations of haemostatic functions (6). A mixture of 1 part citrate with 9 parts

blood is recommended for coagulation tests (1,8). One part citrate is mixed with 4 parts blood to determine the erythrocyte sedimentation rate (1).

2.4.3 Heparinates

To obtain heparinized plasma, unfractionated sodium, lithium or ammonium salt of heparin is recommended at a concentration of 12 to 30 international units (IU)/mL of blood with a molecular mass of from 3 to 30 kD (1). Calcium-titrated heparin at a concentration of 40-60 IU/mL blood (dry heparinization) and 8-12 IU/mL blood (liquid heparinization) is recommended for the determination of ionized calcium (9).

2.4.4 Hirudin

An antithrombin extracted from leeches or prepared by a genetic engineering process. Hirudin binds thrombin to form a 1:1 hirudin-thrombin complex. It is used in a concentration of 10 mg/L (10).

3. PLASMA OR SERUM

3.1 Advantages of using plasma

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

1. **Time saving:** Unlike serum, in which coagulation is not complete until after 30 minutes, plasma samples can be centrifuged directly after sample collection.
2. **Higher yield:** 15 to 20% more plasma than serum can be obtained from the same volume of blood.
3. **Prevention of coagulation-induced interferences:** Regardless of coagulation-induced changes in blood (see below) anticoagulants prevent coagulation of blood or plasma in the primary and secondary container after centrifugation that could cause analytical interference (e.g., clogged sample needle in the analytical system).
4. **Prevention of coagulation-induced changes:** The coagulation process changes the concentrations of numerous quantities in the extra-cellular fluid beyond the maximum allowable limit (11-13). This is induced by the following mechanisms:
 - Increase in the number of platelet components in serum as compared with plasma (e.g. potassium, phosphate, magnesium, aspartate amino transferase, lactate dehydrogenase, serotonin, neuron-specific enolase, zinc). Release of ammonia from fibrinogen induced by Factor XIII.
 - A decrease in the concentration of quantities in serum as a result of the coagulation process (total protein, platelets, glucose).
 - Activation of the cell lysis of erythrocytes and leukocytes in uncoagulated blood (free haemoglobin, cytokines, receptors).

Due to coagulation-induced changes some determinations yield valuable results only when plasma is used (e.g. neuron-specific enolase, serotonin, ammonium).

3.2 Disadvantages of plasma over serum

The addition of anticoagulants can interfere with certain analytical methods or change the concentration of the quantities measured:

- Contamination with cations: ammonium, lithium, sodium, potassium.
- Assay interference caused by metals binding to 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 (9)).
- Interference by fibrinogen in heterogenous immunoassays (12).
- Inhibition of metabolic or catalytic reactions by heparin: e.g. Taq polymerase in the polymerase chain reaction (PCR) (14).
- Interference in the distribution of ions between the intracellular and extracellular space (e.g. Cl^- , NH_4^+) by EDTA, citrate (11).
- Serum electrophoresis can be performed only after pretreatment.

The table below provides information on the utility of anticoagulants for the measurement of analyses in whole blood, plasma or serum.

3.3 Analytical samples in the serological diagnosis of infectious diseases

A variety of methods are used for serological diagnosis of infectious diseases. They include immunodiffusion, immunoprecipitation, counterimmuno-electrophoresis, agglutination of bacteria, haemagglutination and agglutination inhibition, particle-enhanced agglutination complement fixation, indirect immunofluorescence (IFA), enzyme-linked immunoassay (ELISA), radio immunoassay (RIA), neutralization of toxins or virus-activity, immunoblot (Westernblot) and others.

In general, serum is used for the serological diagnosis of infectious diseases; serum must be used for some immunological techniques such as complement fixation or bacterial agglutination tests; for others, such as some haemagglutination tests, ELISAs or immunoblots, serum and plasma can be used likewise. Usually, the commercially available tests are adapted to the use of serum only.

4. RECOMMENDATIONS

The table below indicates materials that are recommended for a specific test. The table also contains information on the utility of other sample materials as long as the measured results by that method do not exceed the maximum allowable deviation of measurement (15). A maximum deviation of 10% is taken as acceptable if the quantity is not included in the current list. In this case, other samples can also be used for the analysis.

4.1 Sample collection and transport time

The following procedure is recommended to avoid contamination when filling tubes (11): blood culture, serum [avoid serum as first tube when electrolytes are to be measured (23)], citrate, heparinate, EDTA, tubes containing additional stabilisers (e.g. glycolysis inhibitors). Only the recommended quantity of anticoagulant should be added, wherever required, to avoid errors in results.

Tilt the tube repeatedly directly after filling to thoroughly mix the sample with anticoagulant (do not shake, avoid foaming). Leave the containers at room temperature for at least 30 minutes to separate serum from non-anti-coagulated samples of whole blood. This period is shorter when coagulation is activated. The length of time to leave the sample at room temperature should not exceed the time recommended by the Working Group for the stability of the quantity in the sample matrix (16).

4.2 Centrifugation

4.2.1 Background

Blood cell constituents can be rapidly separated from plasma/serum by centrifugation (relative centrifugal force, rcf). Rcf and rotations per minute (rpm) can be calculated by using the rotating radius r (the distance between the axis of rotation and the base of the container in mm). The following equation applies:

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

It is recommended to centrifuge blood containers in 90° -swing-out rotors that the sediment surface forms a right angle to the container wall, thus preventing contact between the sampling needle in the analyser and the cell surface or separating gels.

4.2.2 Serum

When coagulation is complete, the sample should be centrifuged for at least 10 minutes at a minimum speed of 1500 g .

4.2.3 Plasma

To obtain cell-free plasma, centrifuge the anti-coagulated blood (citrated, EDTA or heparinized blood) for at least 15 minutes at 2000 to 3000 g . When separating serum or plasma, the temperature should not drop below 15°C or exceed 24°C.

4.3 Storage

Non-centrifuged samples can be stored at room temperature for the time as published in the recommendations on stability (16). After centrifugation, the serum or plasma from primary tubes should be analyzed within the time as indicated in the recommendations for whole blood, if the whole blood sample is stored at room temperature without the use of separating gels or a filter separator. If serum or plasma must be refrigerated or frozen for preservation or because of labile quantities, blood cells must first be separated. Avoid freezing whole blood samples before or after centrifugation, when polymer separating gels are used.

4.4 Evaluation of new analytical procedures

Before using a new reagent or method, check the suitability of the procedure by comparing at least 20 blood samples with normal, and 20 with pathological concentrations of the quantity to be measured. It can be assumed that the criteria for biological and clinical interpretation (reference intervals, clinical decision limits) have changed, if the mean of the difference between the samples tested deviates by more than the maximum deviation allowed (15) or by more than 10%.

5. Table: THE USE OF VARIOUS ANALYTICAL SAMPLES

- ⊕ recommended sample
- + can be used without changes of results
- (+) can be used with limitations [see remarks; in case of citrate plasma this indicates the need to consider dilution by liquid citrate (24)].

Higher (↗) or lower (↘) results may be observed when compared to recommended samples.
A blank field indicates that no data was found from literature.
Greek letters refer to information provided by diagnostic companies.
Numbers in brackets indicate references.

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrate Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Acetaminophen	+	+ α, β, ε	+ α, ε	(+)ε				
Acetylsalicylate	+	+ β	+ β	(+) β				
α ₁ Acid glycoprotein (orosomuroid)	+	+ γ	+ γ	(+)				
Adenovirus-antibodies	+							complement fixation test ELISA IgG, IgM
Adrenocorticotrophic hormone (ACTH)		+	⊕					stabilized with aprotinin 400 kU/mL, mercaptoethanol 2μl/mL
Alanine aminotransferase (ALAT, ALT, GPT)	+	+	+	(+)				
Albumin	+	+*	+	(+)				* bichromatic assays recommended for colorimetric methods (17)
Aldosterone	+	+	⊕					
Alkaline phosphatase	+↗	⊕	-	(+)				EDTA effectively binds essential cofactor zinc
Aluminium	-	-	-	-				special tube
Amikacin	+	+	+β	(+)β				
Amiodarone	+	+	+					HPLC
Amitriptyline	+	+						HPLC
Ammonium	-↗	(+)↗	⊕	-	+			use serine 5 mmol/L and borate 2 mmol/L to prevent in-vitro ammonia formation (18). Do not use ammonium heparinate
Amphetamine	+	+	+					
Amylase, pancreatic	+	+	+	(+)				

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrated Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Amylase, total	+	+	(+) ∇	(+)				possible decrease due to Mg and Ca binding (29)
Androstendione	+							
Angiotensin converting enzyme (ACE)	+		-	-				
α_1 -Antitrypsin	+	+ γ	+ γ					
Anticonvulsant drugs	+							see phenobarbital, valproic acid, phenytoine
Anti-staphylolysin	+	+ γ	+ γ					
Anti-streptodornase B	+							
Anti-streptokinase	+							
Anti-streptolysin	+	+ β, γ, δ	+ β, γ, δ					
Anti-thrombin III	-			\oplus			+*	*test by Pharmacia
Anti-thrombin III immunol.			+ δ	(+) δ				
APC-resistance (genotyping factor V Leiden)					\oplus	\oplus		
APC-resistance (functional screening test)				\oplus				high level of heparin may require addition of heparin-binding substances
Apolipoprotein A1	+ ∇	+ γ, δ	$\oplus \gamma, \delta$	(+)				see NCEP guidelines
Apolipoprotein B	+ ∇	+ γ, δ	$\oplus \gamma, \delta$	(+)				see NCEP guidelines
Aspartate – aminotransferase (ASAT)	+ ∇	\oplus	+	(+)				
Aspergillus antibodies	+							
Aspergillus antigen-detection	+							
Aspergillus, culture isolation								blood culture bottle
Autoantibodies								
Anti-mitochondrial antibodies (AMA)	+							
Anti-neutrophil cytoplasmatic antibodies (ANCA)	+							

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citratd Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Anti-nuclear antibodies (ANA)	+							
Cardiolipin antibodies	+							
Cold-autoantibodies					+?			Native blood in 37°C water bath
DNA antibodies	†							
Thrombocyte antibodies			+	+				
Thyrotropin receptor antibodies (TRAK)	+							
Barbiturates (see also phenobarbital)	+	+						
Bartonella spp. antibodies (cat scratch disease)	+							
Batroxobin time	-	-	-	⊕				
Benzodiazepines	+	+						
Bicarbonate	+	+			⊕			see also blood gases
Bilirubin, direct, total	+	+	+	(+)				
Blood cell surface markers (immunocytometry)					+	+		special stabilizer recommended (Cyfix II) (27)
Blood gases (CO ₂ , O ₂)					⊕			heparinized titrated blood (9)
Bordetella pertussis antibodies	+							
Borrelia burgdorferi-antibodies (Lyme disease)	+							ELISA, Western Blot
Brucella antibodies (Brucellosis)	+							
CA 125	+	+γ	+γ	(+)γ				
CA 15-3	+	+γ	+β, γ	(+)γ				
CA 19-9	+	+γ	+γ	(+)γ				
CA 72-4	+	+γ	+γ	(+)γ				
Cadmium	-		⊕	-				special tube
Calcitonin	+	+						stabilized with aprotinin

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citratd Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
complexes	+							
Clostridium tetani toxin antibodies	+							
Coagulation factors II-XIII	-	-	-	⊕				
Cocaine	+	+			+			
C3-complement	+	+	+γ	(+)γ				
C4-complement	+	+	+	(+)				
Copper	+	+	-	-				special tube available
Corticotropin								see ACTH
Cortisol	+	+	+γ					
Corynebacterium diphtheriae toxin antibodies	+							
Coxiella burnetii antibodies (Q-fever)	+							
Coxsackie-virus antibodies	+							
C-peptide	+	+						
C-reactive protein (CRP)	+	(+) ** +α, ε	(+) * +α, ε	(+)				* method-dependent ** patient-dependent low results
Creatine kinase (CK)	+	+β, δ	+β, δ	(+)				
Creatine kinase MB, enzyme	+	+	-	(+)				
Creatine kinase MB, immunoassay	+	+β, γ, ε	+β, γ, δ, ε	(+)γ				
Creatinine	+	+	+	(+)				
Cryptococcus neoformans								blood culture bottle
Cyclosporin A	-	-	-	-		⊕		
CYFRA 21-1	+	+γ	+γ	(+)γ				
Cystatin C	+	+	⊕					
Cytomegalovirus antibodies	+	+β	+β	(+)β				
Cytomegalovirus antigen (pp 65)	+					⊕		
Cytomegalovirus						⊕		

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrate Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
DNA-amplification								
D-Dimer	-	+	-	⊕				
Dehydroepiandrosterone-sulfate (DHEA-S)	+							
Dengue-virus antibodies	+							
Diazepam	+	+	+					
Differential leukocyte count						⊕		K ₃ or K ₂ EDTA, stability instrument-dependent
Digitoxin	+	+α, β, γ	+ γ					
Digoxin	+	+α, β, γ, ε	+ β, γ	(+) β				
Disopyramide	+	+	+	(+)				
DNA- and RNA-analysis by amplification					-	⊕	+	heparin inhibits Taq polymerase and restriction enzymes (25), LiCl 1.8 mol/L eliminates this error (26)
Dopamine			+					
Echinococcus spp. antibodies	+							
ECHO-virus antibodies	+							
Elastase						+		
Entamoeba histolytica antibodies	+							
Enterovirus-antibodies	+							
Epstein Barr heterophilic antibodies (Paul Bunnell test)	+							
Epstein-Barr-Virus-antibodies (anti-EBNA, -VCA, EA); IgG, IgM, IgA; ELISA	+							
Erythrocyte sedimentation rate (ESR)							⊕	1 part citrate, 4 parts blood
Erythrocytes					+	⊕	(+)	heparin not recommended

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citratd Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Erythropoietin	⊕	+	+					
Estradiol (E ₂)	+	(+) γ	(+) γ	(+) γ				
Estriol (E ₃)	(+)	+						
Ethanol	+	+ β, ε	+ β	(+) β, δ		+		
Ethosuximide	+	+	+					
Fatty acids, free	+	(+) ↗ *	(+) ↘					* activation of lipase by heparin
Ferritin	+	+ β, γ, δ, ε	(+) * γ	(+) γ				* method-dependent
α ₁ -Fetoprotein (AFP)	+	+ β, γ	+ β, γ	(+) β, γ				
Fibrin monomers	-	-	-	⊕				
Fibrin(ogen) degradation products	(+) *	-	-	(+) **				* special tube stabilized with 10 U thrombin and 150 AU kallikrein/mL blood (31) ** aprotinin or soybean trypsin inhibitor, special tube (31)
Fibrinogen, Clauss	-	-	-	⊕				
Fibrinogen immunol.	-	-	-	⊕				
Folate	+	+	+ β	(+) β		+ β		haemolysate prepared by 0.5 blood + 4.5 mL ascorbic acid (2 g/L). Na-heparinate interferes with Axsym test (β)
Follitropin (FSH)	+	+α, β, γ	+α, β, γ	(+) γ				
Francisella tularensis antibodies (tularemia)								
Fructosamine	+	+	+					
FSME virus antibodies	+							
Galactose 1-puridyl-transferase (Beutler Test)						+		erythrocytes
Gastrin	+	⊕ *	+	(+)				* add aprotinin 2000 KIU/mL to stabilize
Gentamicin	+	+ β, γ, δ	+ β, γ, δ	(+) β				
Glucagon			+					stabilized with aprotinin (11)
Glucose	- ↘				(+)			use glycolysis inhibitor

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrate Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Glucose capillary	-	+ ↘	+ ↘		(+)			tube or whole blood with universal glycolysis inhibitor (mannose, fluoride)
Glutamate dehydrogenase	+	+	+					
γ-Glutamyl transferase (IFCC/Szasz)	+	+	+	(+)				
Glycated albumin								see fructosamine
Gold	+							
Glutamate-oxaloacetate transaminase (GOT)								see ASAT
Glutamate-pyruvate transaminase (GPT)								see ALAT
Growth hormone (STH; somatotropin)	⊕	-	-					
Haematocrit					+	⊕		
Haemoglobin A1c						⊕		haemolysate
Haemoglobin F (HbF)						+		
Haemoglobin in whole blood						⊕		
Haemoglobin plasma	(+) ↗	⊕	+					haemolysis during clotting
Hantavirus-antibodies	+							
Hantavirus-DNA-amplification					-	⊕	+	
Haptoglobin	+	+	+					
Helicobacter pylori-antibodies	+							ELISA; immunoblot detection of virulence factors (cag A and others)
Heparin (anti Xa)				⊕				
Hepatitis antibodies								
anti-HAV	+	+ β	+ β	(+) β				
anti-HBsAg	+	+ β, δ	+ β, δ	(+) β, δ				
anti-HBc	+	+ β	+ β	+ β				
anti-Habe	+	+ β	+ β	(+) β				
anti-HCV	+	+ β	+ β	(+) β				
HBsAg	+	+ δ	+ δ	(+) δ				
HBeAg	+	+ β	+ β	(+) β				

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrate Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Hepatitis B virus DNA						⊕		
Hepatitis C virus RNA-amplification, qualitative, quantitative (virus load)						⊕		
Hepatitis C virus genome typing						⊕		
Hepatitis D virus antibodies	+							
Hepatitis D virus RNA-amplification						⊕		
Hepatitis E virus antibodies	+							
Hepatitis E RNA-amplification						⊕		
Heparin-associated thrombopenia; HIPA test	+							
Herpes simplex 1 or 2-virus antibodies	+							
HHV 6 antibodies (human herpes virus 6)	+							
HHV 6, 7, 8 -DNA-amplification						⊕		
HI virus-1 and 2 antibodies (Human immunodeficiency virus)	+	+ β	+ β	(+) β				MEIA ELISA; immunoblot
HI virus-1 RNA-amplification qualitative, quantitative (virus load)			+			⊕		
HI virus-1 (provirus) DNA-amplification						⊕		
HLA-ABC typing					⊕			ammonium-heparinate blood
HLA-B27					⊕	⊕		” “ ”
HLA DR typing						⊕		
Homocystein	+↗	+	+	(+)		⊕		sample with EDTA/acidic citrate (0.5

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citratd Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
								mol/L) (21). Store blood at 0-4°C. Haemolyzed EDTA sample in detergent (22).
HTLV I antibodies (T-cell leukemia)	+							
HTLV I (provirus) DNA-amplification						⊕		
HTLV I RNA-amplification			+					
Human chorionic-gonadotropin (βhCG)	+	+ β, γ	+ β, γ	(+) γ				
Human growth hormone (HGH)	⊕	+						
3-Hydroxybutyrate					+			deproteinized blood
IgA	+	+ γ, δ	+ γ, δ					
IgD	⊕		- ↓, γ					
IgE antigen specific IgE	⊕ +	+ δ, ε	- ↓ + δ, ε	(+) ε				
IgG IgG subclasses	+ +	+ γ, δ	- ↓	-				
IgM	+	+ γ, δ	↓, γ, + δ					
Influenza virus ABC-antibodies	+							
Insulin	(+) ↓	+	+					
Iron (Fe)	+	+	- ↓	- ↓				
JC polyoma virus-antibodies (progressive multifocal leukoencephalopathy; PML)	+							
JC polyoma virus DNA-amplification (PML)						⊕		
Lactate	- ä	- ä	- ä	-	(+)			use glycolysis inhibitor tube (fluoride/oxalate) if not immediately deproteinized in whole blood
Lactate dehydrogenase (LDH)	(+) ↗	⊕	+	(+)				LDH platelet-dependent (11,12)

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrated Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Lead (Pb)	-	-	+	-	(+)			use special tubes
Legionella – antibodies	+							
Leishmania spp. antibodies (Visceral leishmaniosis)	+							
Leptospira spp. antibodies (Leptospiroses)	+							
Leukocyte count					+	⊕	(+)	
Lidocaine	+	+β	+β					
Light chains (κ, λ)	+	+γ	+γ					
Lipase	+	+	↘	-				EDTA binds calcium (activator)
Lipoprotein electrophoresis	⊕	-	-	-				
Lipoprotein (a)	+	+γ	+γ	-γ				
Listeria monocytogenes antibodies	+							
Listeria monocytogenes DNA-amplification						⊕		
Lithium	+	+*	-	-				* do not use Li-heparinate
Lupus anticoagulant	-	-	-	⊕				
Lutropin (LH)	+	+β	+β					
Lymphocyte subtypes					+	(+)		special stabilizer recommended (Cyfix II) (27)
Lymphocytic choriomeningitis virus (LCM) antibodies	+							
Lymphocytic choriomeningitis virus DNA-amplification						⊕		
Magnesium (Mg)	+↗	+	↘	↘	⊕			separate blood cells before analysis (20)
Measles virus antibodies	+							

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citratd Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Measles virus RNA-amplification						⊕		
Mercury (Hg)					+			special tube
Methadone	+	+						
Methotrexate	+							
α ₁ -Microglobulin	+							
β ₂ -Microglobulin	+	+ γ	+ γ	(+) γ				
Microfilaria					+	+		concentrated sample
Morbili virus antibodies	+							
Morbili virus DNA-amplification						⊕		
Mumps virus-antibodies	+							
Mycobacterium spp. DNA-amplification (tuberculosis and atypical mycobacteria)						⊕		
Mycoplasma pneumoniae antibodies	+							
Myoglobin	+	+ γ, ε	+ γ, δ, ε	(+) γ, ε				
Neisseria gonorrhoeae antibodies	+							
Netilmycin	+							
Neuron-specific enolase (NSE)	+↗	⊕						increased by thrombolysis
Nitrazepam	+	+ β	+ β	(+) β				
Opiates	+	+						
Osmolality	+	+						
Osteocalcin	+*	+*	⊕*					* stabilized with aprotinin 2500 kU/mL
Pancreas elastase	+							
Paracetamol	+	+ β, ε	+ β, ε	(+) β, ε				
Parathyrin (PTH)	+ κ		⊕					
Partial thromboplastin time	-	-	-	⊕				

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrate Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
activated (aPTT)								
Parvovirus B19 - DNA-amplification						⊕		
Phenobarbital	+	+ β, γ, δ, ε	+ β, γ, δ, ε	(+)β,γ,δ, ε				
Phencyclidine	+							
Phenytoin	+	+ β, γ, δ, ε	+ β, γ, δ, ε	(+) β, γ, ε				
Phosphate, inorganic	(+) ↗	⊕	+					platelet-dependent in serum (11,12,19)
Plasmodium spp.						⊕		microscopic examination of whole blood
Plasmodium antibodies	+							
Potassium	(+) ↗	⊕	-	-	+			platelet-dependent in serum (11,12,19)
Pneumococcus								blood culture
Prealbumin	+	+ ε	+ γ, ε					
Primidone	+	+	+	(+)				
Procainamide	+	+ β	+ β	(+) β				
N-Acetyl-procainamide	+	+ β	+ β	(+) β				
Procalcitonin	+	+ δ						
Progesterone	+	+ β	+ β					
Prolactin	+	+ β, δ	+ β					
Propaphenone	+	+						
Propoxyphene	+	+						
Prostate specific antigen (PSA), free	+	+ γ, ε	+ γ					
Prostate specific antigen (PSA), total	+	+ γ	+ γ	(+) γ				
Protein C	-	-	-	⊕				
Protein S	-	-	-	⊕				
Protein S 100	+							
Proteins, total	+ ↘	⊕	+ δ	(+)				plasma results higher due to fibrinogen
Prothrombin time (Quick, PT)	-	-	-	⊕				

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrate Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Pyruvate	- ↘	- ↘			+			deproteinized blood
Q-fever antibodies	+							
Quinidine	+	+ β	+ β	(+) β				
Red blood cell count					+	⊕	(+)	
Renin	-	-	+	-				
Reovirus antibodies	+							
Reptilase time								see Batroxobin time
Respiratory syncytial virus (RSV) antibodies	+							
Rheumatoid factors (RF) subfractions IgA, IgG	+		+ γ	(+) γ				
Reticulocyte count					(+)	⊕		K ₂ or K ₃ EDTA, method-dependent
Rickettsia antibodies	+							
Rotavirus antibodies	+							
Rubellavirus antibodies	+	+ β	+ β	(+) β				
Rubellavirus DNA-amplification						⊕		
Salicylate	+	+ α,β,δ,ε	+ β, δ, ε	(+) β, δ				
Sandfly (pappataci-) fever antibodies	+							
Selenium (Se)	-	-	-	-		+		special tubes
Serum amyloid A (SAA)	+							
Serum electrophoresis	⊕	(+)						fibrinogen to be considered when using heparin plasma, may be eliminated
Sodium (Na)	+	+	-	-	+ *			* use 140 mM Na-heparin 8-12 IU/mL blood (9)
Somatotropin (STH)								see growth hormone
Squamous cell carcinoma antigen (SCC)	+							
Staphylococcal antibodies;	+							

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citratd Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
anti-staphylolysin								
Streptococcal antibodies; anti-streptolysin O anti-streptokinase	+							
Streptococcal antibodies; anti B DNase	+							
Streptococcal antibodies, anti-hyaluronidase	+							
Tacrolimus (FK 506)			-	-		⊕		
Testosterone	+	+ γ	+ γ	(+) γ				
Tetrahydrocannabinol-carboxylic acid (THC)	+	+						
Theophylline	+	+ β, γ, ε	+ β, γ, δ, ε	(+) β, γ, ε				
Thrombin time	-	-	-	⊕				
Thrombocyte function							⊕	special tube (27)
Thyrotropine (TSH)	+	+ β, γ, ε	+ β, γ	(+) γ				spot blood in newborns
Thyroglobulin	+							
Thyroid antibodies	+							
Thyroxine (T4)	⊕	+ β, γ, ε	+ β, γ	(+) γ				plasma difference method-dependent
Thyroxine, free (fT4)	+	+ β, γ	+ γ	(+) γ				
Thyroxine binding globulin (TBG)	+	+						
Tick born encephalitis-virus antibodies (FSME)	+							
Tobramycin	+	+ β, δ	+ β, δ	(+) β				
Toxoplasma gondii-antibodies (IgG, IgM)	+	+ β	+ β	+ β				
Transferrin	+	+	+ γ					
Treponema pallidum antibodies	+							TPHA, IFT, FTA, antibodies, VDRL, Immunoblot
Treponema pallidum DNA-amplification						¾		

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citrated Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
Tricyclic antidepressants	+	+ β	+ β	(+) β				
Triglycerides	+	+	$\frac{3}{4}$	(+)				
Triiodothyronine (T3)	\oplus	(+) β, γ, δ						plasma difference method-dependent
Triiodothyronine, free (fT3)	+	+ β, γ	+ β, γ	(+) γ				plasma difference method-dependent
Troponin I	+	+ β, ϵ	+			+		method dependent
Troponin T	+	+ γ	(+) γ					
Trypanosoma gambiense						(+)		ideally, blood film of capillary blood
T-Uptake	+	+ β, γ, ϵ	+ β, γ, ϵ	(+) γ				
Urea	+	+	+					do not use NH_4 heparinate
Urate	+	+	+ \downarrow	(+)				
Valproate	+	+ $\beta, \gamma, \delta, \epsilon$	+ β, γ, δ	(+) β, γ				
Vancomycin	+	+ β, ϵ	+ β, ϵ	(+) β, ϵ				
Varicella Zoster virus antibodies	+							
Varicella Zoster virus DNA-amplification						\oplus		
Vasoactive intestinal polypeptide (VIP)			\oplus^*					* Aprotinine 500-2000 KIU/mL (31)
Vasopressin (ADH)	- \nearrow		\oplus					frozen plasma
Vitamin A (retinol)	+							
Vitamin B1 (thiamin)		+	+					
Vitamin B12 (cobalamin)	+	+ β	$\oplus \beta$					
Vitamin B2 (riboflavin)		+	+					
Vitamin B6 (pyridoxal phosphate)			\oplus					
Vitamin C (ascorbic acid)		+						stabilized with 60 mg/L metaphosphate
Vitamin D, (1,25-dihydroxycholecalciferol; 25-hydroxychole-	+							

Analyte	Serum	Heparinized Plasma	EDTA Plasma	Citratd Plasma	Whole Blood			Remarks
					Hep.	EDTA	Cit.	
calciferol)								
Vitamin E (tocopherol)	+		⊕					
Vitamin K (transphylochinone)								
Yersinia enterocolitica antibodies	+							
Zinc (Zn)	-	+	-	-				special tube, avoid contamination by stopper (28)

Legend:

- α : Ortho: Vitros-system
- β : Abbott: Axsym
- γ : Roche: Hitachi, Elecsys
- δ : Beckman: (partially different specifications) synchron LX/CX Immage Array, Access
- ε : Dade Behring: Nephelometer Analyzer, Dimension/
- κ : DPC Immunlite

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