Immunoelectrophoresis, Serum

Sampling: 1 ml serum

Reference Interval: Report on diagnostic findings
Including immunoglobulins

Immunoglobulin E (IgE)

Related Information: Aspergillus fumigatus, Serology
Eosinophil Count
Histamine, Urine or Plasma

Background: IgE is a monomeric immunoglobulin composed of epsilon heavy chains and two kappa or lambda chains with a MW of 190 kDa, carbohydrate is 12%, serum half life of 2 days. It does not fix complement nor does it cross the placenta. Plasma cells producing IgE are predominantly located along the respiratory and gastrointestinal membrane.

The Fc region binds to the high-affinity IgE receptor on the surface membrane of mast cells and basophils. Bound IgE serves as a receptor for antigens after crosslinking by allergens; mediators such as histamine, prostaglandin D2, kallikrein, leukotrienes C, D and E are released and an immediate type I hypersensitivity reaction occur, which may include urticaria, sneezing, rhinorrhea, conjunctival edema, attacks of asthma and possibly anaphylactic shock. The synthesis is controlled by interleukin-4 and interleukin-13.

Function: Main host defense mechanism against parasites such as Strongyloides, Trichinella, Ascaris, Hookworms. IgE specific for parasite proteins bind to receptors on eosinophils and trigger antibody dependent cellular cytotoxicity (ADCC) response.

In atopic disease levels exceed 400 IU/mL, very high levels > 1000 to 20000 IU/mL may be reached in bronchopulmonary aspergillosis, asthma, atopic eczema, IgE myeloma, and parasitism. The level of IgE does not strongly correlate with atopy; it may be in the upper normal range.

Elevated cord blood levels may predict atopy in later life.

Sampling: 2 mL serum.

Reference Interval: (1 IU =2.4 ng protein)

Adult:	< 100 IU/mL
Cord blood:	< 2.0 IU/mL
Newborn:	< 1.0 IU/mL
Children:	
up to 1 year:	< 16 IU/mL
1 – 2 years:	< 29 IU/mL
3 – 4 years:	< 58 IU/mL
5 – 7 years:	< 79 IU/mL

Immunoglobulin A (IgA), Serum, Saliva, CSF

Related Information: Cryoglobulin, Qualitative, Serum or Plasma
Endomysial Antibodies
Gliadin IgG/IgA Antibodies
Immunoglobulin G (IgG), Serum, Urine, CSF
Immunoglobulin G Subclasses (IgG subclasses)
Protein Electrophoresis, Serum and Protein, Total, Serum

Background: About 6% of the serum immunoglobulins are IgA class and play a major role in mucosal immunity. IgA class immunoglobulins are secreted with milk, colostrum, saliva, tears, and into the respiratory and intestinal system. The mechanism of action includes inhibition of adherence of microorganisms to the surface of mucosal cells. As a multivalent immunoglobulin with high avidity of binding to antigens it is relevant in neutralization of viruses and in combining with antigens in food, preventing absorption and allergic reactions.

IgA fixes complement in the alternative pathway, has opsonizing properties for phagocytosis through an Fc receptor on macrophages, it induces eosinophil degranulation, linking it to anti-parasitic response.

Half life 5 to 6.5 days; daily synthetic rate is 24 mg/kg/day; the placenta is not crossed. Useful in evaluation of humoral immune status. Used to evaluate lymphoproliferative diseases such as multiple myeloma and `Mediterranean` lymphoma with bowl involvement. IgA myelomas are characterized by IgA > 2g/L, hypercalcemia, hyperviscosity and 25% of the patients present a monoclonal IgA.

IgA may be decreased in chronic sinopulmonary diseases, ataxia telangiectasia in congenital IgA deficiency associated with autoimmune diseases and antibodies to IgA.

In Berger disease, an IgA glomerulonephritis, 50% of the patients present with elevated serum IgA.

IgA deficiency is associated with chronic diarrhoea, giardiasis, celiac disease, with autoimmune diseases such as rheumatoid arthritis.

Sampling: 2 mL serum, 1 mL saliva, 1 mL CSF. If cryoglobulinemia or macroglobulins are expected, sample should be kept at 37°C.

Reference Interval for Serum:

Children: (g/L)	male	female
1-30 days	0.01-0.22	0.01-0.19
1 month - 6 month	0.07-0.56	0.01-0.59
6 month - 1 year	0.09-1.07	0.015-0.9
1-3 years	0.18-1.71	0.25-1.41
4-6 years	0.60-2.31	0.47-2.06
7-9 years	0.77-2.52	0.41-2.18
10-12 years	0.61-2.69	0.73-2.39
13-15 years	0.42-3.04	0.82-2.96
16-18 years	0.89-3.14	0.90-3.22
Adults: (g/L)	0.7-3.8	

Alternative Reference Interval for Serum (g/L)

	mean white male	mean white female
20-24 years	1.32	1.28
25-29 years	1.4	1.35
30-34 years	1.5	1.42
35-39 years	1.59	1.49
40-44 years	1.7	1.59
45-49 years	1.81	1.65
50-54 years	1.3	1.74
55-59 years	2.06	1.83
60-64 years	2.2	1.93
65-69 years	2.34	2.03
70-74 years	2.49	2.14
>75 years	2.66	2.26

Reference Interval for Saliva: 20-200 mg/L

Reference Interval for CSF: 2-6 mg/L

Immunoglobulin G (IgG), Serum, Urine, CSF

Related Information: Immunoglobulin G Subclasses (IgG subclasses)
Protein, Total, Serum

Background: Heavy chain classification of immunoglobulins leads to five classes with IgG class displaying the highest plasma concentration. Polyclonal gammopathy is seen in chronic inflammatory or autoimmune diseases. Plasma cell myeloma, lymphoma or non malignant conditions may be related to monoclonal gammopathy. The quantitation is useful in monitoring IgG myeloma, evaluate humoral immunity, and follow up immunodeficiency states. The monoclonal IgG fraction is elevated to more than 3 g/dL in approx. 60% of the cases of multiple myeloma.

Sampling: Serum: 1 mL serum, stable for 5 days at 4˚C. CSF: 1 ml CSF.
Urine: A 10 ml aliquot of a 24 h urine collection is required, please note total quantity.
Suspected samples for macroglobulins or cryoglobulins should be held at 37˚C. Samples suspected for cold agglutinins serum should be separated prior to cooling to 4˚C.

Reference Interval for Serum: (mg/dL)

	age	male	female
Children:	1-30 days	260-980	220-1031
	31-182 days	195-643	390-794
	183-365 days	184-974	407-774
	1-6 years	550-1400	600-1500
	13-15 years	709-1860	891-1900

Adults: 564-1765 mg/dL

Reference Interval for Urine: < 15 mg/24 h
Reference Interval for CSF: < 4 mg/dL

Immunoglobulin G Subclasses (IgG subclasses)

Related Information: Immunoglobulin A (IgA), Serum, Saliva, CSF
Immunoglobulin G (IgG), Serum, Urine, CSF
Protein, Total, Serum

Background: IgG immunoglobulins account for 80% of all immunoglobulins. Selective deficiencies despite of normal overall IgG occur in patients presenting recurrent infections, antibody responses within certain subclasses are linked to certain types of pyogenic infections. IgG2 deficient patients present with recurrent respiratory infections. Selective IgG1 deficiency was reported to be associated with sino-respiratory diseases and caused by S. pneumoniae and Hemophilus sp. IGA together with IgG2 and IgG4 deficiencies were linked to phenytoin therapy. IgG4 was found to be increased in sclerosing pancreatitis.

IgG subclass	1	2	3	4
Percent of total IgG	65%	23%	8%	4%
Half life time (days)	21	21	8	21
Complement fixation	moderate	weak	strong	none

Sampling: 2 mL serum
Reference Interval: (mg/dL)

Age (years)	IgG1	IgG2	IgG3	IgG4
0-1	190-620	30-140	9-60	6-60
1-2	230-710	30-170	10-100	5-40
2-3	230-830	40-240	5-130	3-120
3-6	350-810	50-310	9-160	5-180
older than 6	270-1740	30-630	10-320	11-620

Immunoglobulin M (IgM)

Related Information: Cold Agglutinin Titer
Cryoglobulin, Qualitative, Serum or Plasma
Protein Electrophoresis, Serum
Protein, Total, Serum
Rheumatoid Factor, Serum

Background: IgM has a large molecular mass of 900 daltons, which limits the immunoglobulin to the vascular compartment. It is a pentamer of 7S gamma globulin. IgM accounts for 5-9% of the total immunoglobulins and account for cold agglutinins, isoagglutinins and most types

of rheumatoid factors. It binds complement and the initially produced antibody in immune response. IgM is the first antibody class produced by the fetus. It does not cross the placenta in contrast to the IgG type.

Low IgG, IgA and IgE levels with marked increased IgM occur in the hyper-IgM combined primary immunodeficiency syndrome. Patients develop infections with encapsulated bacteria and intracellular organisms such as Pneumocystis carinii, Cryptosporidium parvum and Leishmania species.

Waldenstrom's disease is characterized by weight loss, anemia, hyperviscosity, hepatosplenomegaly, lymphadenopathy, epitaxis and by IgM macroglobulins with IgM levels > 3g/mL.

In contrast myeloma derived immunoglobulins are monoclonal IgG or IgA type.

IgM is increased in primary biliary cirrhosis in addition to elevated alkaline phosphatase and antimitochondrial antibodies.

Decreased levels of IgM occur in congenital or acquired hypogammaglobulinemias.

Sampling: 1 mL serum, if cryoglobulins or macroglobulins are expected, keep sample at 37°C.

Reference Interval: (mg/dL)

	Age	male	female
Children:	1-30 days	12-117	19-104
	31-182 days	27-147	9-212
	183 d - 1 year	27-197	4-216
	1-6 years	63-240	70-298
	7-9 years	49-231	62-270
	10-12 years	58-249	81-340
	13-18 years	57-298	69-361

Adults: 53-375 mg/dL

Influenza Type A and B, Serology

Background: Influenza viruses are the only member of the small, 110 nm in diameter, segmented-single stranded RNA orthomyxoviruses. The envelope is covered with spikes of hemagglutinin and neuramidase. The hemagglutinin binds to the cell surface receptor and is also target for neutralizing antibodies.

Influenza A causes worldwide epidemics and pandemics every 10-20 years, influenza B causes major outbreaks. Transmission via respiratory droplets, incubation period 1-2 days. Complications: Bacterial pneumonia, Reye's syndrome, characterized by encephalopathy and liver degeneration in children following viral infections such as influenza and chickenpox.

There is no lifelong immunity, but vaccines.

Sampling: 1 mL serum, sample at onset and reconvalescent serum

Reference Interval: Differentiation of immunoglobulin class

IgA antibody	negative:	< 0.7 COI
	borderline:	0.7–1.0 COI
	positive:	> 1.0 COI
IgG antibody	negative:	< 20 RE/mL

Insulin, Serum

Related Information: Ammonia, Plasma
Glucose, Blood, Urine, Liquor
Insulin-Like Growth Factor Binding Protein 3 (IGF-BP3), Serum
Insulin Resistance
Albumin, Urine

Background: From the precursor protein preproinsulin three hormones are derived: proinsulin, insulin, and C-peptide.

Hypoglycemia may be caused by islet cell tumor, exogenous insulin, hypoglycemic drug, alcohol, pituitary or adrenal insufficiency, and severe hepatic impairment. In children, persistent hypoglycemia of infancy (PHHI) has to be considered.

Useful in hypoglycemic disorders:

- PHHI presenting without ketosis or acidosis during infancy. Serum glucose < 54 mg/dL, serum insulin >10 µU/mL, increased C-peptide and increased proinsulin. The most severe form presents immediately after delivery, the less severe form during childhood. A third form is characterized by hyperammonemia.
- tumor-induced hypoglycemia is caused by islet cell tumor, most of the tumors are benign.
- hypoglycemia as a secondary phenomenon in patients with carcinomas.

Sampling: Patient should be in a fasting state. 2 mL serum, freeze immediately, ship to laboratory frozen.

Reference Interval:	Infants	0-13 mU/L
	Adults	6-25 mU/L

Insulin Auto-Antibody Human (IAAb), Serum

Related Information: Insulin, Serum

Background: Preceding or manifestation of diabetes mellitus type I, antibodies to insulin occur age dependent. In children < 5 years IAAb prevalence is 90%-100% whereas > 12 years prevalence decrease to 40%.

Useful in the predictive diagnostic marker for diabetes mellitus type I.

IAAb is tested positive in 2% of first degree relatives of diabetes type I patients. In combination with tyrosine phosphatase IA-2 autoantibody, pancreatic isle cell autoantibody, glutamic acid decarboxylase (GAD65) autoantibody, the predictive value increases to 80%-100% for type I diabetes

mellitus if at least three of the autoantibodies are tested positive. If 2 autoantibodies are tested positive, 25% develop a diabetes mellitus within 10 years, if one antibody is present, 10%.

Sampling: 1 mL serum

Reference Interval: < 1.0 U/mL

Insulin-Like Growth Factor-1 (IGF-1), Serum or Plasma see Somatomedin C, Serum or Plasma (IGF-1)

Insulin-Like Growth Factor Binding Protein 3 (IGF-BP3), Serum

Related Information: Insulin, Serum
Somatotropin
Somatomedin C

Synonyms: Somatomedins

Background: At least 10 different IGFBPs are known. The serum concentrations are proportional to the amount of circulating growth hormone. IGFBP-3 has a long half life time and binds 95% of IGF in the blood. Besides transporting IGFs, it plays a role in apoptosis.

Sampling: 1 ml serum, stable for 2 days at 4°C.

Reference Interval:

Children	0.9–4.2 µg/ml
Male	1.7–6.7 µg/ml
Female	2.0–7.3 µg/ml

Insulin Resistance

Related Information: Glucose, Blood, Urine, CSF
Insulin, Serum

Background: The HOMA model for insulin sensitivity allows to calculate the degree of beta cell function and the degree of peripheral insulin response. Therapeutic approaches may be adjusted to the major cause either to decreased insulin secretion or to impaired peripheral insulin sensitivity.

There are more than 500 studies using the HOMA formula for assessing insulin resistance or sensitivity (IR or IS).

Studies include the investigation of longitudinal changes in beta cell function and IR in patients with diabetes to evaluate the natural history of the disease or treatment regimes (sulfonylureas, metformin, and diet). Large scale epidemiological studies have been done to evaluate various ethnic groups with glucose intolerance. The large scale Bruneck Study concluded HOMA as a predictor for true insulin sensitivity comparable to the intravenous tolerance test.

Useful parameter:
- for individuals with abnormal glucose tolerance to track changes in insulin sensitivity and beta cell function.
- in individuals with abnormal glucose tolerance to assess the balance of insulin sensitivity and beta cell function, indicating whether reduced insulin sensitivity or beta cell failure predominates.
- in collecting longitudinal data in subjects who may develop abnormal glucose tolerance.
- if used with a careful interpretation in individuals on insulin secretagogues.

An initial increase in beta cell function in subjects on sulfonylurea may be followed by a decline, reflecting the secretagogue mechanism without amelioration of the rate of beta cell failure.
Limitations: HOMA can not be used in patients taking exogenous insulin. A clinical view always has to be taken into consideration, that for example a thin and fit individual with an overshooting high sensitivity of 200% to insulin may display a beta cell function of only 50%.
The model is validated within a range of 1-2000 pmol/L insulin or 1-25 mmol/L glucose.

Sampling: 2 mL serum for insulin level (freeze immediately, ship to laboratory frozen) and 1 mL blood in sodium fluoride tube for blood glucose level.

Reference Interval: There are no standardized reference ranges

HOMA % Beta cells function (HOMA % B)	110% - 90%
HOMA % Insulin Sensitivity (HOMA % IS)	90% -110%

Interleukin 6 (IL-6)

Related Information: C-Reactive Protein, Serum
Fibrinogen, Functional
Plasminogen, Plasma

Background: IL-6 is an immune, hematopoietic and proinflammatory cytokine, secreted as a 184 amino acid peptide of 21 kDa, mapped on chromosome 7 and synthesized by T and B cells, monocytes, as well as by macrophages, fibroblasts, keratinocytes, synoviocytes, chondrocytes and endothelial cells. IL-6 acts receptor mediated on T cells, hepatocytes, hematopoietic progenitor cells and neuronal cells. It stimulates B cells to differentiate, stimulates osteoclast formation, proliferation of vascular smooth muscle cells induces platelet derived growth factor production, induce fever by affecting the hypothalamus and induces as one of the proinflammatory cytokine IL-1, IL-6 and TNF the production of acute phase proteins by the liver. IL-6 acts synergistically with IL-1, IL-3, IL-5, IL-9, IL-11, GM-CSF, G-CSF on Burst Forming Unit-Erythrocyte and on Colony Forming Unit-Erythrocyte-Granulocyte-Macrophage. IL-6 acts also on Colony Forming Unit-Megacaryocyte to increase platelet production. IL-6 stimulates human myeloma cells to proliferate. In the CNS IL-6 supports survival of cholinergic neurons, in the reproductive system, it induces secretion of human chorionic gonadotropin from trophoblasts.
IL-6 may be used in patients with rheumatoid arthritis, with a significant correlation synovial fluid

concentration of IL-6 and IgG. It may play a role in development of membranoproliferative glomerulonephritis fond in patients with systemic lupus erythematosus. It may pal a role in diabetes type I and in plasmocytomas. It is helpful in differentiation between septic cause of fever or drug induced fever in patients on chemotherapy.

Sampling: 2 mL serum, separate immediately in refrigerated centrifuge, freeze and ship frozen.

Reference Interval: < 5.4 pg/mL

Intrinsic Factor Antibody (IFA)

Related Information: Folic Acid, Serum
Homocysteine, Plasma
Methylmalonic Acid, Serum or Plasma or Urine
Vitamin B_{12}, Plasma or Serum

Background: Intrinsic Factor (IF) is a 62 KD glycoprotein secreted at a rate of 50-100nmol per liter of gastric juices. Pernicious anemia is a common cause of vitamin B_{12} deficiency and is associated with antibodies to parietal cells and intrinsic factor autoantibodies. There are 2 types of autoantibodies against IF known:

A) Type I or blocking antibody which binds competitively to the vitamin B_{12} binding site of the IF. The antibody in the serum is of class IgG, the antibody is directly secreted into the gastric juice is of IgA class inhibiting the uptake of vitamin B_{12} in the ileum. 70% of the patients suffering from pernicious anemia develop type I antibodies.

B) Type II which binds to the vitamin B_{12}–IF complex. Type II antibodies are not pathogenic, but are associated with pernicious anemia in 35% of the patients and in 50% of the patients when type I antibodies are present.

False positive results are rarely reported in Graves' disease and atropic gastritis. Parietal cell antibodies are less specific for pernicious anemia although present in up to 90% of the patients.

Sampling: 1 mL serum, stop vitamin B_{12} medication 3 days prior to blood collection.

Reference Interval: Antibodies Typ I: not detectable

Iron (Fe), Serum

Related information: Copper, Serum or Urine
Erythropoietin (EPO), Serum
Ferritin, Serum or Plasma
Occult Blood in Stool (Hemoccult)
Porphyrins, Quantitative, Urine or Stool
Transferrin and Total Iron Binding Capacity, Serum

Background: Please see also Transferrin, Serum.

Iron is essential for oxygen and electron transport ($Fe2^+/Fe3^+$) and as a metal cofactor for enzymes. Hemoproteins are involved in oxygen binding and metabolism (peroxidase, catalase,

oxidase, cytochrome); nonheme proteins (iron cofactor function) are involved in mitochondrial actionase, DNA synthesis (ribonucleotide reductase), required for collagen, tyrosinase and catecholamine metabolism. Iron has effects on cell mediated immunity.
Distribution: Overall iron is estimated to be 40-50 mg per kg body weight. 30 mg exists in the form of hemoglobin. 5-6 mg in women and 10-12 mg in men exists in iron stores (ferritin, hemosiderin), 6-7 mg in tissue, in myoglobin, heme-enzymes and non-heme-enzymes. < 0.2 mg is bound to transferrin.
Regulation: Iron is not excreted by the body, besides small amounts in bile, urine, sweat, occult loss into the gastrointestinal tract or uterine loss. Daily loss is less than 1 mg in men, in women 1.5 mg. Recommended daily intake for men 10 mg, for woman 18 mg. Absorption only in the $Fe2^+$ form mainly in the duodenum with an absorption rate of 5%-10% of dietary iron which can be increased up to 20%-30% in a deficient state.
After absorption, iron is bound to transferrin. Cells acquire iron from transferrin by the transferrin receptor (TfR), a transmembrane glycoprotein that is predominant in all cells and particularly in placenta, liver and erythroid precursor cells.
The average value for plasma iron is 18 µmol/L, total iron binding capacity 56 µmol/L, transferrin saturation 35%. Total plasma pool of iron is estimated to 3 mg, iron stores to 350–900 mg. (man at the upper and woman at the lower limit)

Overview on iron status indicators changes:

Status	Ferritin	Transferrin	Serum Iron	Iron Saturation
Iron deficiency	down	up	down	down or normal
Anemia in chronic diseases	up or normal	down or normal	down	down or normal
Sideroblastic anemia	up	down or normal	up or normal	up
Hemolytic anemia	up	down or normal	up	up
Hemochromatosis	up	normal or down	up	up
Acute liver impairment	up	variable	up	up
Protein deficiency	down	down or normal	down or normal	

Iron deficient states are caused by inadequate absorption due to celiac disease, inflammatory bowl disease, bowl resection, dietary, intrinsic red cell defects or to increased iron loss due to tumors, varices, gastritis, ulcer, and parasites.
Overload occurs either in a state were erythropoiesis is normal but iron binding capacity of transferrin is exceeded and iron is deposited in the liver and into other organs or when iron is overloaded by transfusions and macrophages take up the excess of iron.
Limitations: In infectious, inflammatory or malignant disease transferrin saturation and iron concentrations may be decreased but are not indicating a deficient state. Total iron binding capacity (TIBC) and transferrin are increased with normal saturation in patients on oral contraceptives
Deferoxamine interferes with TIBC. TIBC is falsely overestimated during highly free iron levels.

Sampling: 1 mL serum, EDTA plasma not accepted. Avoid hemolysis. Fasting sample is preferred in the morning, there is a circadian rhythm, low in the evening, up to 30% higher in the morning. Stable for 1 week at 4˚C.

Reference Interval: 48–152 µg/dL for adult males
5-10% lower for adult females

Iron (Fe), Urine

Related Information: Hemolysins
Glucose-6-Phosphate Dehydrogenase (G6PD), RBC
Hemoglobin Electrophoresis
Hemoglobin, Qualitative, Urine
Iron and Iron Binding Capacity/Transferrin, Serum
Lactate Dehydrogenase (LDH), Serum

Background: In case of intravascular destruction of blood, free hemoglobin alpha-beta dimers are bound to haptoglobin and removed from the circulation by the live parenchymal cells if plasma hemoglobin levels exceeds 50-200 mg/dL (the binding capacity of haptoglobin for hemoglobin). The dimers of hemoglobin are filtrated by the glomeruli and a portion is reabsorbed by the tubular cells. The tubular cells convert hemoglobin to hemosiderin. If the tubular cells are shed into the urine, hemosiderinuria occurs. Hemoglobinuria occurs if the tubular reabsorption capacity is exceeded. Hemoglobin not bound to haptoglobin or not excreted by the kidney is oxidized to hemiglobin and the oxidized heme groups are bound to hemopexin, a beta globulin. The complex is cleared by hepatic parenchymal cells. If hemopexin is depleted, hemin groups bind to albumin, forming methemalbumin.
Useful in the assessment of intravascular hemolysis, hemochromatosis, hemolytic anemia, nephrotic syndrome, paroxysmal nocturnal hemoglobulinuria, multiple transfusions.
Limitations: Hemosiderin is shed in the urine several days after onset of hemolysis with slow decline, which may take weeks to month after heart valve replacement.

Sampling: A 5 mL aliquot of a 24h urine collection. Note total quantity.

Reference Interval: 3–99 µg/24h

Iron Total Binding Capacity see Transferrin and Total Iron Binding Capacity, Serum

Jo-1 Antibody

Related Information: Antinuclear Antibody
Scl-70 Antibody
SS-A/Ro and SS-B/La Antibodies

Synonyms: Antihistidyl Transfer tRNA Synthetase