

# Curriculum Clinical Chemistry The Netherlands

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### 1. Year 1 (Foundation year)

In general it can be said that all items mentioned in year 1 are only relevant to those parameters which need to be known for acute diagnostics.

#### Compulsory components: see also description below

- Internship IC, 5 working days
- Internship A&E, 5 working days
- Internship local blood bank, 0.5 working day
- Courses Sanquin transfusion

#### Compulsory techniques:

- spectrophotometry
- flame photometry
- osmometry
- nephelometry
- turbidimetry
- enzyme kinetics
- centrifugation
- cell counts (simple flow cytometry)
- haemocytometry (impedance and optical measurements)
- coagulation tests
- agglutination techniques
- solid-phase techniques
- column techniques
- microscopy

#### General analytical aspects belonging to all analytes from year 1.

##### Pre-analysis

- Physiological variation
- Preparation of patient
- Medication
- Blood collection

- Anticoagulants
- Sample processing
- Storage conditions
- Interfering factors

#### Interpretation

- Reference values
- Age-gender dependence
- Significance of abnormal results

#### Decision-making aspects

- Sensitivity/Specificity
- PPV/NPV
- ROC-curves
- Incidence/prevalence

#### Standardization

- Reference values, reference materials, reference methods, IFCC recommendations

#### Quality

- Notions (quality assurance, quality system, Quality control, Quality assessment, Quality Assurance)
- To be able to assess internal quality controls
- Shewhart charts, Westgard rules
- To be able to assess external schemes (CCKL/SKML)
- Laboratory evaluations (correctness, precision, accuracy, linearity, detection limit, recovery, carry-over, analytical specificity)
- Comparison of methods (plots, regression, statistics)

### **Clinical Chemistry**

#### Analytical aspects:

- Spectrophotometry, flame photometry, osmometry, nephelometry, turbidimetry, equilibrium constants, dissociation constants, enzyme kinetics, centrifugation.

#### POCT

- Pre-analytical aspects, interfering factors, used techniques.

#### Liver:

- Analyses and interpretation of ALAT, ASAT, GGT, AF, Bilirubin, Albumin, coagulation factors.
- Physiology, synthesis, exocrine functions
- Pathophysiology, acute hepatitis, chronic hepatitis, cirrhosis, cholestasis, gallstones, steatosis, medication.

#### Pancreas:

- Analyses and interpretation of amylase, lipase, p-elastase, chymotrypsin.
- Physiology, exocrine functions
- Pathophysiology; acute pancreatitis, chronic pancreatitis, pancreatic insufficiency.

#### Gastrointestinal tract:

- Anatomy

#### Heart:

- Analyses and interpretation of Troponin T and I, CK/CKMB, LDH, Myoglobin, ASAT, (NT-pro)BNP
- Physiology
- Pathophysiology: Myocardial infarction, heart failure.

#### Kidney/Fluid and electrolyte balance:

- Analyses and interpretation of creatinine, urea, osmolality, Na, K, Cl, bicarbonate, PO<sub>4</sub>, Calcium, urine test.
- Comprehension: effective circulating volume, osmolality
- Physiology; GFR, clearance, potassium homeostasis, sodium homeostasis, influence of glucose
- Pathophysiology:
  - Hyper/Hyponatraemia: serious hyperglycaemia, osmotic diuresis, kidney failure, lack of volume, natriuretic peptides
  - Hyper/Hypokalaemia; redistribution (influence glucose), kidney failure, metabolic acidosis and K, extrarenal loss
  - Acute kidney insufficiency
- Operating principle of the 3 main diuretics; LIS-diuretics, Thiazide diuretics, Potassium sparing diuretics.

#### Acid-base disorders:

- Analyses and interpretation of a blood gas, Henderson-Hasselbach, O<sub>2</sub>-saturation curve
- Physiology: regulation equilibrium, role of kidneys, role of lungs, gas exchange, O<sub>2</sub> transportation, anion gap
- Pathophysiology: Acidosis/Alkalosis, Metabolic/Respiratory, compensation.

#### Remaining body fluids:

- Urine diagnostics; stick, sediment, interpretation and clinical relevance
- Liquor: Analysis cells, bilirubin (spectrum), glucose; to distinguish viral versus bacterial meningitis, to recognise subarachnoid haemorrhage.
- Ascitic fluid; transudate/exudate, origin of unknown fluid in the abdomen
- Pleural effusion
- Chyle

#### Immunology:

- Acute phase response (ferritin, albumin)
- CRP/BSE

### **Haematology**

#### **General**

##### Haematopoiesis

- Theoretical knowledge of haematopoiesis

##### Haemocytometry

- Principles of haemocytometry equipment
- Pitfalls in measurements with the help of haemocytometry equipment
- Interpretation of normal results of the haemocytometry-analyzer
- Interpretation of uncomplicated abnormalities of the haemocytometry-analyzer.

##### Morphology of normal blood cells

- To know when to perform a manual differentiation (safe/not safe)
- To be able to assess from a normal blood profile
- To differentiate safe/not safe in respect of results haemocytometry-analyzer

#### Quality control

- To be able to assess the quality controls of the haemocytometry
- To be able to assess the quality controls of the morphology

#### Haematology of benign disorders:

##### Benign abnormalities of red blood cells:

#### Anaemia

- To be able to complete the diagnostics of anaemia
- To know the tests which are of importance in anaemia diagnostics; Hb, MCV, iron status, vitamin status, reticulocytes.
- To be able to interpret the data from a modern haematology machine (in so far it concerns the anaemia diagnostics)
  - Pathophysiology: microcytic anaemia:
    - Fe-deficiency (to ascertain and interpret), infections/autoimmune, intoxications, Hb-pathy (to know only of these subjects that 'this can be a cause, no complete diagnosis').
  - normocytic anaemia:
    - acute blood loss (to ascertain and interpret), bone marrow problems (to know hereof only that this can be a cause, no complete diagnosis)
  - macrocytic anaemia:
    - vitamin B12/folic acid, alcohol (to ascertain and interpret), MDS (to know only that this can be a cause, no complete diagnosis)
- To be able to interpret the data of a microscopic assessment of the RBB and to be able to perform this by oneself to some degree.

#### Haemolytic anaemia

- To be able to diagnose haemolysis;
- To know the tests which matter in the diagnosis of haemolysis (direct Coombs, bili, LDH, haptoglobin, reticulocytes).
- Some knowledge of further diagnostic possibilities

##### Benign abnormalities of white blood cells:

#### Granulocytopenia/Neutropenia

- To recognise the disorder, in relation to the blood profile.
- To know which differential diagnosis would be appropriate.

#### Lymphopenia

- Viral infections

#### Leukocytosis

- Neutrophilia
  - Bacterial infection
  - Left shift
  - Leukemoid reaction

- Lymphocytosis: monotone versus polymorphic

**Malignant abnormalities of white blood cells:**

- To recognize a possible haematological malignancy in respect of result haemocytometry.
- To recognize a possible haematological malignancy in respect of manual differentiation.

**Haemostasis I (fundamental)**

**Coagulation:**

Thrombocytes:

- Morphology, counting methods and QC, pre-analytical variables
- Pseudothrombopenia
- Limits for thrombocytes transfusion

General:

- In vivo and in vitro coagulation schemes, fibrinolysis

Analysis techniques:

- Bleeding time, PT, APTT, fibrinogen, d-dimer and PT-INR
- Pre-analytical variables and QC

Pathology

- Diagnostics (suspicion) thrombosis; d-dimer
- Fundamental diagnostics DIS; PT, APTT, thrombocytes, fibrinogen

Therapy:

- Operation and supervision of commonly used anticoagulation agents; prevention and treatment
- Thrombolytics

**Transfusion medicine**

Legislation and Haemovigilance:

- Directive Blood transfusion

Donor selection and donor screening:

- To exclude risks for donors and patients
- Donation procedure
- Global knowledge of laboratory investigation into infectious diseases of donor blood

To prepare/preserve blood and blood products:

- The importance of the conditions under which collected blood products have to be supplied
- Preservation techniques
- Shelf life of blood products
- Change in quality of blood product by processing into finished product
- Assessment of quality of finished product
- Global knowledge of manufacturing processes for blood products with a short or long shelf life
- Which finished products with which indication can be prepared from which blood products

Compatibility tests:

- Principle and scope of the different compatibility tests
- Knowledge of ABO and Rhesus systems
- Compatibility investigation in case of absence of irregular antibodies
- Type and screen versus complete crossmatch
- The meaning of positive Direct Antiglobulin Test
- Transfusion advice with regard to clinically relevant blood groups
- Thorough knowledge of ABO and Rhesus systems
- Compatibility investigation in case of irregular antibodies
- Transfusion advice in case of irregular antibodies
- Transfusion advice in case of the necessity to freezing autologous blood

#### Irregular antibodies:

- Distinction of regular and irregular antibodies
- Distinction of Direct and Indirect Antiglobulin Test
- Knowledge of TRIX
- Knowledge of all relevant blood group systems
- Identification and meaning of irregular antibodies
- To perform and interpret the results of a simple immunohaematologic investigation

#### Transfusion of blood products:

- Indications for the administration of blood products with a short shelf life
- Product specifications of all blood products with a short shelf life
- The issue of the correct blood product for the correct indication
- Knowledge of the transfusion policy in special circumstances (such as massive blood loss, refractoriness)
- Knowledge of complications in the administration of blood products
- To give advice to and to accompany at exchange transfusions

#### Transfusion reactions:

- Knowledge concerning the laboratory follow-up with all forms of (alleged) transfusion reactions
- Reporting to TRIP
- Advice concerning recognizing and treating of transfusion reactions

#### Pregnancy:

- Advice concerning the administration of anti-D
- Pre and post natal immunohaematological investigation

#### Tuition together with Sanquin:

Short internship at the local blood bank. (This concerns an internship of a half to a whole day with the aim to gain an insight in the donor screening and the operation of the local blood bank. A nationwide internship description will be made, to which small in-depth assignments are allocated.)

Module operation from modular training transfusion medicine Sanquin, 1 day

Module IHD IIA from modular training transfusion medicine Sanquin, 2 days.

### **Endocrinology**

In general it can be said that in year 1 all items mentioned under endocrinology are only relevant to those parameters which need to be known for acute diagnostics. In year 1 there is no need to be familiar with mutation analysis. The tumour markers in all mentioned subtopics are only discussed from the second year onwards.

*Pre-analysis focused on endocrinological analytes.*

Because the resident (Clinical Chemistry) will be confronted early on in the training with pre-analytical problems of the entire fundamental module endocrinological analytes, it is necessary that the knowledge of the pre-analysis goes further than only the cito applications within the endocrinology.

- Physiological variation

To be familiar with the variation in concentration of hormones, such as the time of day of collection (day/night rhythm of eg cortisol), phase of the menstrual cycle and pregnancy (oestradiol, progesterone, LH, FSH), puberty (sex steroids), age. Hormone concentrations vary strongly with gender and during various phases in life: pregnancy, puberty, childhood, old age.

Rhythmic excretion during the day of many hormones. Seasonal variation for 25-OH-vitamin D. Reference values for FT4 and TSH are dependent on iodine status of the reference population.

- Preparation of patient

For the cortisol analyte one needs to know the effect of eg stress, exertion. The effect on the aldosterone/renin analyte of eg lying down/standing up.

- Collection of blood/urine

General knowledge of collection conditions. Collection in cooled tubes and fast centrifugation and freezing (eg catecholamines, ACTH). Effects of freezing-thawing: destruction of fragile hormones. The occasional necessity to use protease inhibitors. For urine: morning portion or 24 hour sample of urine for eg cortisol.

- Anticoagulants

Use of EDTA, heparin or blood collection tubes. Interference of too high concentrations of anticoagulants in sample on immunoassay.

- Sample processing

Effect of processing on the stability of the hormones such as ACTH, catecholamines. Cryo activation renin.

- Storage conditions

- Stability of blood and plasma/serum at various temperatures. The effect of freezing and thawing: FT4 rises

- Interfering factors (Pitfalls, organ dependent interference, medication)

- Medication

To be familiar with the interference by medication, such as thyreostatica, Thyrax and Cytomel (synthetic T3) on the TSH/FT4 analyte, hydrocortisone and prednisolone on the cortisol analyte, effect of very high or low protein concentrations on steroid analytes and effect of oestrogenic contraceptives on binding proteins (eg CBG and TBG).

- Standardization (Reference material; dependence of isoforms)

- Standardization aimed only at the cito-parameters, such as cortisol, prolactin, TSH, FT4,  $\beta$ HCG, and AFP. In the case of prolactin this also includes the method dependency of isoforms. WHO reference materials. Composition thereof: purified preparation, recombinant technique. Commutability of these materials.

Analytical aspects:

- Knowledge of the analytical aspects of and the differences between immunoassays and immunometric assays. The existence of interference by macroprolactin, heterophile antibodies and high dose hook effects must be known and which actions are necessary to exclude or to get round this.
- Laboratory evaluations  
Method comparisons (analytical) for the TSH, FT4 and cortisol analyte

#### Endocrine control systems:

- To know in general which types of control systems (feed-back loops) exist.

#### Hypophysis & Hypothalamus:

- Anatomy and physiology
- Regulation and functions
- Prolactinoma and diagnostics thereof.

#### Thyroid:

- Anatomy and physiology  
Manufacture of the hormones TSH, T4 and T3, as well as the feedback mechanism.
- Diagnosis Hypo and hyperthyroidism  
The diagnosis hyper/hypothyroidism needs to be set, whereby the importance of the cito FT4 in the context of the Congenital hypothyroidism (CHT) screening needs to be understood. Causes of hypo/hyperthyroidism are discussed in year 2/3.

#### Bone metabolism:

- Calciumhomeostasis; role of PTH, vitamin D
- Phosphatehomeostasis
- Knowledge of the analytes PTH, vitamin D

#### Adrenal gland:

- Anatomy and physiology
- Extensive knowledge of the cortisol analyte, as well as indications for a cito-cortisol.

#### Diabetes mellitus and obesitas:

- Endocrine pancreas function
- Hormonal regulation glucose metabolism. Place of insulin and glucagon.
- Division and classification diabetes mellitus  
Type I DM is an autoimmune disease whereby the pancreas no longer produces insulin. With type II the hyperglycaemia is caused by insulin resistance of tissues and in the second instance a decrease in production of insulin of the pancreas. Obesity is a risk factor in developing type II DM.

#### Lipid metabolism:

- Physiology of the lipid metabolism (endogenous and exogenous lipid transport)
- Knowledge of the laboratory analytes LDL/HDL/TG/apo's

#### Fertility:

- Indications for cito  $\beta$ hCG/AFP (hCG: pregnancy hormone and (almost ideal) tumour marker).
- Understanding of the physiology of the hypothalamus-hypophysis-gonad axis in women and men.
- Adrenarche and menarche are only discussed in the second year.

#### Special physiology

- Pregnancy
- Interference of pregnancy regarding the cito-parameters.

### **(Hereditary) Metabolic diseases**

- Knowledge of laboratory analytes lactate, ammonia, glucose, blood gas, ketones (see also chemistry).
- Knowledge of preliminary investigation KCL that can denote a metabolic disease (but not which metabolic disorder).
- Neonatal screening: logistics and consequences

### **Clinical Internships**

I Clinical internship Accident and Emergency (one consecutive week, after at least 6 months training)

Learning objectives:

- Has knowledge of the state of affairs of the A&E (organization, nature of patients, contacts with specialists, contact with the laboratory and the possible bottlenecks)
- Knows how the application of laboratory applications comes about
- Knows of the possibly present POCT facilities and of the bottlenecks
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Activities:

- To shadow one of the doctors (registrar or specialist)
- What is triage and what is the purpose?
- To take note of the protocols present and in particular the laboratory aspects (are these still up to date?)
- Regard for the communication with the house and the laboratory in particular

Result:

- The assistant composes a short report regarding the possible points of improvement between A&E and laboratory and discusses these with the responsible Clinical Chemist and supervisor.

II Clinical internship Intensive Care (one consecutive week, after at least 6 months training)

Learning objectives:

- Has knowledge of the state of affairs in intensive care (organization, nature of patients, contacts with specialists, contact with the laboratory and the possible bottlenecks)
- Knows how the laboratory results are interpreted
- Knows of the possible POCT facilities, usage thereof and the possible bottlenecks

Activities

- To shadow one of the doctors (registrar or specialist)
- Takes part in the morning report/transfer
- To take note of the laboratory aspects in the protocols used
- Attention to the communication with the laboratory
- If possible, to take part in training for assistants focused on acute care

Result

- The assistant composes a short report regarding the possible points of improvement between IC and laboratory and discusses this with the Clinical Chemist responsible and the internship supervisor of the IC.
- If there was a definite assignment during this week it is recommendable to finish the week with a lecture by the resident (Clinical Chemistry) for the doctors working in IC.

## 1. 2nd/3rd Year (In-depth knowledge phase)

In general it can be said that all items mentioned in years 2/3 cover the parameters which every laboratory specialist clinical chemistry must know.

### **Compulsory components: see description below**

- Internship OR, year 2, 5 working days
- Internship Internal Medicine, year 2, 10 working days
- Internship Paediatrics, year 3, 5 working days
- Internship Gynaecology, year 3, 5 working days
- Internship Hereditary Metabolic Diseases, 1 month EMZ laboratory UMC
- Management course
- Quality course
- Answering audience questions, 2 x 1 week, end of 3rd year
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### **Knowledge of the principles of the following techniques:**

- Flowcytometry
- Western Blotting
- PCR
- Sequence analysis
- HPLC
- Gas chromatography
- (tandem) mass spectrometry
- Binding analysis
- Electrophoresis
- IR spectroscopy
- Immuno electrophoresis
- Radial immunodiffusion
- Gel diffusion
- Immunoblotting

Analytical aspects:

- Specialized techniques; iso-enzymes, macro-enzymes.

Liver:

- Analyses and interpretation of ALAT, ASAT, GGT, AF, Bilirubin, Albumin, coagulation factors.
- Pathophysiology; extensive bilirubin metabolism

Pancreas:

- Pathophysiology; pancreatic carcinomas, cystic fibrosis.
- Function tests

Gastro-intestinal tract:

- Anatomy
- Pathophysiology; diarrhoea, malabsorption, coeliac disease (Transglutaminase, HLA-DQ2, DQ8), intestinal failure, Irritable Bowel Syndrome (Crohn/Colitis Ulcerosa), bacterial overgrowth,
- Function tests; among other things xylose, H<sub>2</sub>-breath test, Lactose Tolerance Test
- Quantitative faeces investigation

Kidney/Fluid and electrolyte balance:

- Pathophysiology:
  - Nephrotic syndrome, chronic renal insufficiency, dialysis - methods

Nervous system:

- Extensive liquor diagnostics (protein spectrum, leakage, Tau protein).
- MS, meningitis, interpretation subarachnoid haemorrhages
- Protein spectrum

Oncology/Tumour markers (see also endocrinology):

- PSA
- Ca 125
- Ca 15-3
- Ca 19-9
- Remaining markers for monitoring

Iron metabolism:

- Haemochromatosis (HFE gene mutation analysis)

Main aspects of remaining body fluids:

- Faeces, amniotic fluid, semen, sweat, synovial fluid, nasal discharge, saliva, tear fluid, lymphatic fluid, pancreatic fluid, bile (including aspect gallstones), breastmilk, abdominal fluid.

## **Immunology**

General:

- function and diagnostic meaning of acute phase proteins (positive and negative), immunoglobulins, complement factors
- acute phase reaction, prevention and diagnostics
- physiology of the immune system: humoral and cellular
- analyte ANA, anti-DNA, anti-ENA, arthritis factors and complement factors

Specialized diagnostics:

- immunoglobulins, classes and sub-classes
- classification auto-antibodies of positive ANA and anti-ENA
- analyte and meaning ANCA of vasculitides
- analyte organ specific auto-antibodies
- circulating immune complexes
- meaning of HLA-B27 for diagnosis rheumatic diseases

Clinical backgrounds:

- hereditary and acquired immunodeficiencies
- systemic autoimmune diseases: SLE, RA, Sjögren syndrome
- organ specific autoimmune diseases

## Allergy

General:

- type I to IV allergic reaction
- mechanism of hypersensitivity
- release of mediators and their effect on target cells

Specialized diagnostics:

- analyte of total IgE and allergen specific IgE
- skin tests
- cross reactivity
- precipitating antibodies

Clinical backgrounds:

- atopic reactions
- medication oversensitivity
- serum sickness
- hyposensibilisation

## Medical Genetics

General:

The to be acquired knowledge includes the general aspects, method and application of molecular genetics and the techniques used therein, use of relevant databases and main aspects of the medical genetics namely molecular genetics, cytogenetics, biochemical genetics, family and population genetics.

In the diagnostics of many disorders molecular genetics play an important role. Substantive knowledge of the specific analytes and the place of this analyte with respect to other diagnostics is treated under the concerning clinical subjects. In this part an approach is chosen which points in particular to the specific place of these analytes with respect to other laboratory analytes.

Theory and practice Clinical Chemistry:

- To be aware, and to be able to apply this knowledge, of the diagnostic possibilities and limitations of molecular diagnostics.
- Legislation and regulations with respect to molecular diagnostics, clinical genetics, LOD and networking

- Advice towards clinic with respect to applications molecular diagnostics
- Notions: PCR, Real Time PCR, sequencing, micro-array, SNP's and mutations
- Fundamental diagnostics at the Clinical Chemistry Laboratory: application, implementation, interpretation of results, pitfalls, reports, internal QC, external QC, consultation of applicants etc.

On the basis of the analytes below an impression can be obtained of subjects which are specific to molecular diagnostics:

Haemochromatose (in particular HFE gene mutation analysis)

- Determination methods
- Predictive value DNA analyte and other analytes
- Necessity of duplo analytes
- Family research

Cystic fibrosis (in particular CFTR gene)

- Determination methods
- Place of DNA diagnostics when making the diagnosis
- Screening with the help of CFTR gene with respect to screening with sweat test
- DNA diagnostics at a Clinical Chemistry Laboratory versus diagnostics at a department Clinical Genetics
- Pharmacogenetics (in particular TPMT, CYP2D6, CYP2C9, CYP2C19, VKORC1 etc.)
- Determination methods
- Translation of genotype to phenotype
- The role of pharmacogenetics in relation to other diagnostic possibilities such as analyte level
- Advice of clinical chemist, relation with pharmacist and applicant.

#### **Clinical Genetics:**

- Internship at the outpatients clinic Clinical Genetics (shadowing a clinical geneticist at the clinic)
- Visit to a regional department Clinical Genetics/Medical Genetics

#### **Haematology**

##### **1. Haematology of benign disorders:**

##### **Benign abnormalities of red blood cells:**

Hb-pathy/thalassaemia

- To be able to recognize a synthesis imbalance in one of the globin chains by means of accepted parameters
- To know the definition of a haemoglobinopathy and the most important variations (S,C,D,E)
- Some background knowledge of the clinical profile of the disease
- Some knowledge of the further diagnostic possibilities

Erythrocytosis

- To be able to distinguish between primary and secondary erythrocytosis
- Some knowledge of the further diagnostic possibilities

## **Benign abnormalities of white blood cells:**

### Granulocytopenia/Neutropenia

- Benign: Neutropenia/monopenia
  - production or destruction disruption by medication
- Malignant: marrow bone infiltration by metastasis of (solid) tumours/leukaemia/lymphomas, MDS: see "Haematology of malignant diseases"

### Lymphopenia

- Immune deficiencies: congenital/acquired (HIV, AIDS)

### Leukocytosis

- Eosinophilia
- Basophilia
- Monocytosis

### Dysfunctions of lymphocytes

- Acquaintance with notions below:
  - Pathophysiology of the immune system
  - Defence and inflammatory reactions
  - Autoimmune diseases: tolerance
  - Allergy: TH1 versus TH2-immune response

## **1. Haematology of malignant disorders:**

### Acute leukaemia

- Types of leukaemia (lymphatic/myeloid)
- To be able to apply WHO-classification
- To be able to assess independently peripheral blood morphology (uncomplicated picture)
- Bone marrow diagnostics morphology (to watch)
- Different stain techniques (to watch)
- Flowcytometry (to watch)

### Chronic leukaemia

- To be able to apply WHO-classification
- To be able to assess independently peripheral blood morphology (uncomplicated picture)
- Bone marrow diagnostics morphology (to watch)
- Different stain techniques (to watch)
- Flowcytometry (to watch)
- Blast crisis (lymphatic/myeloid)

### Hodgkin's disease

- To be able to apply WHO-classification
- Bone marrow diagnostics, role of aspirate (to watch)

### Non-Hodgkin's Lymphoma

- To be able to apply WHO-classification
- Bone marrow diagnostics aspirate (to watch)
- Flowcytometry blood/bone marrow/gland (to watch)

## M. Kahler, MGUS, Lymphoplasmacytic lymphoma

- WHO-classification; how to distinguish each
- Bone marrow diagnostics aspirate (to watch)
- Criteria, role of protein spectrum, free kappa/lambda, b2-microglobulin
- Flowcytometry (to watch)

## MDS:

- To be able to apply WHO classification
- To name dysplastic peripheral blood
- Bone marrow diagnostics morphology (to watch)
- Different stain techniques (to watch)

## Chronic myeloproliferative disorders:

- To be able to apply WHO classification of the different disorders
- Morphology of bone marrow diagnostics (to watch)
- Differential diagnosis, what needs to be excluded before the diagnosis may be made.

## Haemostasis

### Coagulation:

### Thrombocytes:

- Megakaryopoiesis
- Classification thrombopenia and thrombocytosis
- Conceptualization with regard to acquired and congenital abnormalities

### General:

- Coagulation cascade including most important physiological inhibitors

### Analysis techniques:

- Determining of the thrombocyte function (PFA)
- Determining of factor deficiencies
- Determining of inhibitor deficiencies
- Determining of LAC and anticardiolipin

### Pathology:

- LAC
- Conceptualization with regard to DIS, HUS, TTP
- Conceptualization with regard to haemophilia and von Willebrand's disease

### Therapy:

- Therapy in deficiencies

## Endocrinology

#### Pre-analysis:

- Preparation Collection (fasting, lying down/standing, speed of processing samples, cessation of medication)
- In-depth knowledge of interfering factors (pitfalls, organ dependent interference, medication)
- Day/night rhythm, month/season dependency of the (sex) hormones
- Pulsatility

#### Standardization:

- WHO reference materials. Composition thereof: purified preparation, recombinant technique.
- Commutability of these materials.
- Used techniques as reference method.
- Harmonization in the case of lack of WHO standards
- Calculation method: the influence on the calibration curves

#### Analytical aspects:

- Laboratory evaluations  
Method comparisons (analytical and clinical) for the remaining endocrinological analyte
- Knowledge of Low-dose hook effect
- Knowledge of the extraction and purification techniques
- Knowledge of use of chromatography and mass spectrometry in endocrinology
- Knowledge of dialysis methods (free versus bound fractions)

#### General:

- Knowledge of the various tumour markers and the kinetics
- Knowledge of synthesis, transport and metabolism of the
  - various peptide hormones (structure)
  - steroid hormones
  - remaining hormones
- Knowledge of mechanism of hormone action (receptors and second messengers)

#### Hypophysis & hypothalamus:

- Evaluation of the axes
- Function tests in relation to the end organ
- Knowledge of the various tumours of the hypophysis
- Causes of hypopituitarism

#### Thyroid:

- Knowledge of the various causes of Hypo and hyperthyroidism

#### Bone metabolism:

- In-depth knowledge of the regulation and pathophysiology of Ca/phosphate metabolism (production and operation of the mediators PTH, calcitonin and vitamin D)
- Knowledge of the role of Mg in the regulation of Ca/phosphate metabolism (Mg homeostasis)
- Knowledge of primary, secondary and tertiary hyperparathyroidism
- Knowledge of primary and secondary hypoparathyroidism
- Knowledge of the pathophysiology of osteoporosis and osteomalacia

#### Adrenal gland:

- Knowledge of the synthesis in the adrenal gland, and the regulation of glucocorticoids, mineralocorticoids and androgens.
- Knowledge of adrenal cortex pathology
- The importance of the cito 17-OH progesterone in the context of AGS screening needs to be understood

#### Endocrine hypertension:

- Conn's syndrome, pheochromocytomas.
- Knowledge of RAAS (see also fluid/electrolyte balance)

#### Fluid/Electrolyte balance

- Aldosterone metabolism, ADH-volume regulation
- Hyper/Hyponatraemia: diabetes insipidus, primary polydipsia, water deprivation test
- Hyper/Hypokalaemia: aldosterone insensitivity

#### Diabetes mellitus and obesitas:

- In-depth knowledge of the hormonal regulation of glucose metabolism.
- Knowledge and causes of insulin resistance
- Diagnostics of insulinoma

#### Growth and development:

- Physiology growth/development child
- Knowledge of growth disorders
- Physiology of puberty
- Disorders of puberty (diagnostics of too early and too late onset of puberty)

#### Lipid metabolism:

- Physiology of lipid metabolism (endogenous and exogenous lipid transport)
- Knowledge of the laboratory analytes LDL/HDL/TG/apo's
- Knowledge of disturbed lipid metabolism

#### Fertility:

- Hormonal regulation of the fertility of men and women
- Causes pathology hypothalamic-hypophyseal-gonadal axis of women and men
- Knowledge of diagnostics ovarian reserve
- Hirsutism and virilization
- Classification PCOS and diagnostics
- Ovulation induction with attention to hyperstimulation syndrome; role of ultrasound scan versus oestradiol measurements
- Knowledge of IVF/EUG/MOLA/testicular tumours
- Knowledge of the parameters to be measured in semen analysis

#### Special physiology

- In-depth knowledge of physiological changes in women in the case of pregnancy

#### Molecular diagnostics

- Familiarity with the general organ dependent mutations underlying the clinical profiles mentioned in the second year.
- Knowledge of the techniques used in endocrinological diagnostics:
  - blotting, PCR, sequencing, fragment analyses (RFLP)
  - Analysis unknown deletions: SNP-array and MLPA

### **Casuistry year 2/3:**

At the end of year 2/3 two cases per clinical profile (organ) must be worked out. The learning objectives must be indicated herein by the registrar.

### **Metabolic diseases**

**Introduction fundamental diagnostics:** there is no presumption that knowledge of individual clinical profiles will be acquired

Compulsory internship of 1 month in Hereditary Metabolic Diseases laboratory UMC

- Logistics Hereditary Metabolic Diseases laboratory
- Hereditary patterns
- The notions preliminary investigation, fundamental diagnostics, enzyme diagnostics, DNA-diagnostics, prenatal diagnostics and neonatal screening
- Neonatal screening in the Netherlands

The significance in relation to hereditary metabolic diseases of:

- hypoglycaemia with or without ketose,
- hypo and hyperuricaemia/uricosuria
- metabolic acidosis
- hyperammonaemia
- crystalluria
- megaloblastic anaemias
- hypo and hypercholesterolaemia

General knowledge\* of defects in the metabolism of:

- carbohydrates (galactosaemia, glycogen storage diseases)
- amino acids (PKU, tyrosinaemia, cystinuria, homocystinuria, urea cycle disorders)
- organic acids (branched chain organic aciduria)
- creatine (GAMT deficiency and creatine transporter defect)
- fatty acid oxidation
- respiratory chain
- N-glycosylation
- metabolic causes of kidney stones
- general knowledge of porphyrias

### **Clinical Internships**

Clinical Internship OR (2nd year, 1 week)

Learning objectives

- Has knowledge of the state of affairs surrounding pre operative screening
- Knows how the responsibilities of the different actors in the OR are allocated (anaesthetist/surgeon)
- Has knowledge of the protocols and the logistics surrounding the ordering and using of blood products in the OR
- Has an impression of the way in which patients are monitored by the anaesthetist during operations
- Knows of the possibly present POCT facilities, the use of these and the possible bottlenecks

#### Activities

- To shadow at the out patients clinic for pre operative screening
- To take note of the planning process in the OR
- To watch (with the anaesthetist) at a few operative procedures with emphasis on the monitoring of the patient
- To take note of the protocols surrounding pre operative screening, order surgical blood, large blood loss and POCT

#### Result

- The assistant composes a short report about the possible points of improvement between the OR and laboratory and discusses this with the Clinical Chemist responsible and the internship supervisor (anaesthetist) of the OR.

Clinical Internship Internal Medicine (2nd year, 2 weeks; 1 week internal medicine and 1 week oncology)

#### Learning objectives:

- Has knowledge of the state of affairs on the wards of internal medicine (organization, nature of patients, contacts with specialists, contact with the laboratory and the possible bottlenecks)
- Has an impression of the most common problems on the ward
- Has an impression of the contribution of the laboratory results on the diagnosis of the patient
- Has an impression of the contribution of the laboratory results on the treatment of the patient.
- 

#### Activities:

- To shadow one of the doctors (registrar or specialist)
- To attend patient discussions and major visits
- To take note of the protocols in place and in particular the laboratory aspects (are these still up to date?)
- Attention to the communication with the house and the laboratory in particular.
- 

#### Result:

- The assistant composes a short report about the role of the laboratory results in the diagnosis and the treatment and hereby indicates points which could improve this. This report is discussed with the supervisor.

Clinical Internship Gynaecology (3rd year, 1 week)

#### Learning objectives:

- Becomes acquainted with the different fields within gynaecology, namely: reproductive medicine/fertility, gynaecological oncology and obstetrics.

- Knows how the laboratory results are interpreted
- Has an impression of the contribution of the laboratory results to the treatment of the patient.

Activities:

- Takes part in patient discussions and clinics of the concerning areas (2 days reproductive medicine/fertility; 2 days oncological gynaecology; 1 day obstetrics)
- To take note of the laboratory aspects in the protocols used (are these still up to date?)
- Attention to the communication with the house and the laboratory in particular

Result:

- The assistant composes a short report about the role of the laboratory results in the diagnosis and the treatment of patients. This report is discussed with the supervisor.

Clinical Internship Paediatrics (3rd year, 1 week)

Learning objectives:

- Has knowledge of the state of affairs on the wards of paediatrics (organization, nature of patients, contacts with specialists, contact with the laboratory and the possible bottlenecks)
- Knows how the laboratory results are interpreted
- Has an impression of the contribution of the laboratory results on the treatment of the patient.

Activities:

- To shadow one of the doctors (registrar or specialist)
- Attends patient discussions/transfer/assistants' teaching time and major visits
- To take note of the laboratory aspects in the protocols used (are these still up to date?)
- Attention to the communication with the house and the laboratory in particular
- 

Result:

- The assistant composes a short report about the role of the laboratory results in the diagnosis and the treatment and hereby indicates points which could improve this. This report is discussed with the supervisor.
- If there was a definite assignment during this week it is commendable to finish the week with a lecture from the registrar for the doctors working on the ward.

## 1. Specialization phase: modules

### A) General

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This part of the training specialization takes place; this follows years 1 and 2. The total duration of this phase amounts to 1260 hours. The specialization phase consists of three modules each of 420 hours, of which 380 are practice and 40 theory. The choice of these modules is voluntary. Six months before commencing the modules, the resident Clinical Chemist must present the syllabus for year 3 and 4 to the Registration Commission (RC). The modules cannot be started until given permission by the RC. If opting

for enrolment in the area of focus (haematology, endocrinology or hereditary metabolic diseases) then all three modules belonging to this choice must be followed. Subsequently a 5<sup>th</sup> year must be followed before registration in the area of focus: the fellowship.

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#### **b) Modules**

- Haematology A: Benign Haematology
  - Haematology B: Lymphatic disorders
  - Haematology C: Myeloid malignancies
  - Endocrinology A: Adrenal gland and gonads
  - Endocrinology B: Thyroid, bone metabolism, parathyroid glands
  - Endocrinology C: Growth, development and energy metabolism
  - Hereditary Metabolic Diseases A: Fundamental diagnostics
  - Hereditary Metabolic Diseases B: Continuation fundamental diagnostics
  - Hereditary Metabolic Diseases C: Enzyme diagnostics
  - Paediatrics
  - Primary care
  - Acute and intensive care
  - Management
  - Point of Care Testing
  - Immunology
- 

#### **4. Fellow year**

Starting points for the syllabus of the 5th year are as follows:

1. The 5th year serves primarily as an experience year; this applies in particular to Endocrinology and Hereditary Metabolic Diseases. For Haematology additional requirements apply which are shown below. After the three modules are successfully accomplished, following permission of the RC, a fellow year can be started. The fellowship year must be accomplished within five years after obtaining the three modules. The fellow year may be extended over no more than 4 years.

### **Additional syllabus haematology:**

It is possible that one or more of the subjects below have been addressed in the modules. In that case these subjects do not need to be treated again in this year. This needs to be indicated in the training schedule.

#### ***Transfusion:***

##### *Donor selection and donor screening:*

- More detailed knowledge of laboratory investigation of donor blood, including HLA/HPA characterizations
- Theory of stem cell donations: stem cells and transplantations
- Apheresis techniques
- 

##### *Compatibility tests:*

- Is able to advise practising doctors regarding specialist investigation in eg TRALI or NAITP
- 

##### *HLA and histocompatibility:*

- Knowledge concerning donor selection on the basis of cross reactivity, acceptable and unacceptable HLA antigens
- To advise on product choice in blood transfusion in the different phases of treatment with stem cells
- 

##### *Transfusion reactions:*

- Knowledge of theory and practice of therapeutic apheresis

##### *Stem cells and transplantations:*

- Thorough knowledge concerning techniques, physiological effects and complications in stem cell apheresis
- Advice concerning product choice with regard to blood transfusion in stem cell treatments and transplantations
- Follow up of allogeneic stem cell transplantations (among others chimerism investigation)
- 

##### *Accompanying courses Sanquin:*

- a. Stem cells
- b. Apheresis I (+II)

#### ***Coagulation:***

##### *Thrombocytes:*

- Assessment megakaryopoiesis in bone marrow and blood
- Causes/classification thrombocytosis and thrombopenia and thrombopathy

*General:*

- Complete physiology of the haemostasis
- (inter)national protocol implementation
- 

*Analysis techniques:*

- Analyte of inhibitors of factors
- Analytes for assessment of fibrinolysis
- 

*Pathology:*

- Thrombopathy
- Haemophilia and von Willebrand's disease
- Other factor deficiencies
- Inhibitors coagulation system

*Therapy:*

- Therapeutic options for different causes of bleeding and thrombosis

**Benign abnormalities of the erythrocyte:**

*Erythrocytic disorders:*

In-depth knowledge of PK, G6PD and other erythrocytic enzymatic defects and membrane abnormalities.

*Hb pathy:*

In-depth knowledge of rarer forms and combinations of Hb variants and thalassaemia.

*Iron Overload:*

In-depth knowledge of rarer acquired and hereditary causes of iron overload.

*Erythrocytosis:*

In-depth knowledge of rarer causes of erythrocytosis.

*Therapeutic possibilities for disorders mentioned above.*

**Bone marrow disorders:**

*Granulocytopenia/Neutropenia*

- In relation to aplastic anaemia: ionizing radiation, chemical substances, medication, serious viral infections
- 

*Bone marrow failure*

To take note of the prevention of rare disorders such as:

- Fanconi's anaemia
- Diamond Blackfan anaemia
- Congenital Dyserythropoietic anaemia
  - Theory disorders
  - Clinical symptoms (theory) and presentation fundamental diagnostics (blood profile, differentiation etc)
  - Bone marrow morphology
  - Confirmatory diagnostics (clinical genetics)

○

#### *Acquired aplastic anaemia*

- Theory disorder
- Clinic, presentation with fundamental diagnostics (Blood profile, dif etc)
- Bone marrow cytology and biopsy (special attention with dd. hypoplastic MDS)
- Treatment and relation with other disorders such as PNH and acute leukaemia.
- 

#### *Leukocytosis*

- More rare causes of lymphocytosis, such as:
  - Whooping cough
  - Autoimmune lymphoproliferative syndrome
  -

#### *Function disorders of phagocytes (granulocytes/monocytes)*

- In depth knowledge of the normal phagocytosis in blood and bone marrow and acquired and hereditary abnormalities thereof, such as haemophagocytosis and Chediak-Higashi syndrome.

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#### *Flowcytometry in MDS*

- Flowcytometrical assessment of dysplasia, abnormal maturation of aberrant markers.

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#### *Flowcytometrical assessment Minimal Residual Disease*

- MRD measurements using aberrant markers. Determination of Leukaemia Associated Phenotypes and the assessment of remission.

#### *Molecular and cytogenetic diagnostics in haematological malignant disorders*

- Prognostic value of the different molecular disorders in leukaemias and lymphomas
- Technical aspects of the analytes and sensitivities
- Possibilities for use of MRD

Theoretical knowledge of cytogenetical disorders and the prognostic value thereof

## Appendix

### Model Training Schedule

Subject		in hours
1 <sup>st</sup> year	Introduction	80
	Clinical Chemistry	630
	Haematology I	300
	Transfusion Medicine	420
	Haemostasis I	95
	Endocrinology/Hereditary Metabolic Diseases I	155
	Clinical internships IC and A&E	80
	Knowledge test fundamental	40
	<b>Subtotal</b>	<b>1800</b>
Subject		In hours
2 <sup>nd</sup> year	Clinical Chemist on duty (present at daytime)	80
	Quality management and assurance; CCKL directive, and others*	60
	Quality course	40
	Scientific research, startup	250
	Information technology, logistics*	70
	Management, planning and control*	100
	Clinical internship II: internal medicine, OR (including patient discussions)	150
	Management course part 1	25
Subject		In hours
2 <sup>nd</sup> or 3 <sup>rd</sup> year	Clinical chemistry	600
	Immunology	300
	Haematology II:	300
	Hereditary Metabolic Diseases II including internship UMC	300
	Endocrinology II	400
	Haemostasis II	130
	Medical Genetics	80
Subject		In hours
3 <sup>rd</sup> year	Knowledge test in-depth knowledge	40
	Clinical internship 3: gynaecology and paediatrics (including patient discussions)	150
	Scientific research continuation	150
	Clinical chemist on duty daytime and support (Clinical chemist on call)	140
	Management course part 2	25
	Reply to audience questions	10
	Responsibility of lab unit	200
	<b>Subtotal year 2 + 3</b>	<b>3600</b>
Subject		In hours
4 <sup>th</sup> year	Responsibility of lab unit continuation	200
	Scientific research, completion	180
	Option module 1 (name)	420
	Option module 2 (name)	420

	Option module 3 (name)	420
	Test option modules	40
	Project to choose	120
	<b>Subtotal year 4</b>	<b>1800</b>
	<b>Total</b>	<b>7200</b>
	<b>Fellow year (not compulsory)</b>	<b>1800</b>
	<b>Total</b>	<b>9000</b>

\* Subjects should be addressed throughout the entire course.