POZNAN UNIVERSITY OF MEDICAL SCIENCES
CHAIR OF CHEMISTRY AND CLINICAL BIOCHEMISTRY
DEPARTMENT OF CLINICAL BIOCHEMISTRY
Head: Prof. Lech Torliński MD, PhD

address**: 60 –780 Poznań**
ul. Grunwaldzka 6
Collegium Chemicum

tel. **+ 48 61 854 6590**
fax. **+ 48 61 854 6599**
e-mail. **lechtor@amp.edu.pl**

Laboratory Medicine: **www.chembiochklin.amp.edu.pl**
60-529 Poznań, ul. Dąbrowskiego 79/601 – Collegium A. Wrzoska, tel.: +48 61 854 6850 (51) fax: +48 61 854 6857

A Guide to Laboratory Medicine

for 3rd year Students of the 4 year MD English Language Program

2006/2007 Academic Year

GROUP B

A U T H O R S :

Prof. Lech Torliński MD, PhD	**e-mail: lechtor@amp.edu.pl**
Sylwia Dzięgielewska MD	**e-mail: syladzie@hotmail.com**
Dorota Formanowicz MD	**e-mail: doforman@amp.edu.pl**
Hanna Kara-Perz MD	**e-mail: hkp@op.pl**
Waldemar Myszka MD	**e-mail: wmyszka@amp.edu.pl**
Ewa Wysocka MD	**e-mail: ewysocka@amp.edu.pl**
Miłosława Zowczak-Drabarczyk MD	**e-mail: mzowczak@amp.edu.pl**
Wojciech Żak MD	**e-mail: wojzak@amp.edu.pl**

C O P Y R I G H T

PART I
A guide to the course

Introduction to the Course of Laboratory Medicine

Dear Students!

In the contemporary medicine an enormous progress is observed in the field of the understanding of diseases' pathogenesis and natural course. That makes it possible to draw up the new diagnostic and therapeutic methods. One of many diagnostic tools of crucial importance in the modern medicine is Laboratory Medicine. Laboratory tests are widely used to make the proper diagnosis, to estimate disease's advance as well as to monitor the therapy results. When performed in selected subjects as the screening tests they enable the early diagnosis of many diseases in the asymptomatic stage. For the other hand the clinical practice often shows ineffective use of laboratory tests which are ordered too frequently with no relation to the clinical situation generating artificial costs of health-care. The tests results are also often improperly interpreted leading to misdiagnosis what might be even harmful to a patient.

The aim of the Laboratory Medicine course is to get the practical skills of proper selection and interpretation of laboratory tests. The laboratory tests and the rules of their results interpretation are presented in relation to the patients' history and the physical examination mainly in the form of the clinical cases analysis. This way you'll get the ability how to match the lab tests with the given clinical picture.

The course consist of a few thematic blocks referring to the basic laboratory tests of hematology, nephrology, gastroenterology, cardiology, endocrinology, neoplastic disorders, disorders of lipid metabolism, water-electrolyte and acid-base balance and newly introduced concerning inflammation and infectious diseases. The separate exercise is devoted to the age-dependent characteristics of laboratory tests.

As the discussion of all topics listed above makes no sense without the basics of physiology, pathology and biochemistry, you are expected to be prepared for the classes following the guide you are reading. The guide consists of the information what should be reviewed before the exercise, what is the topic of the seminar and what are the abilities the student should posses after finishing it. "Review" consists of the outline of the seminar (in details) prepared by the leading teacher with all the slides, graphs and pictures presented during the seminar as well as the suggested readings.

The first part of each seminar is the discussion of the laboratory test in the relation to the physiology, pathology, biochemistry, clinical history and physical findings. This way your preparation to the seminar is ascertained. The theoretical part is followed by the analysis of the clinical cases related to the discussed topic. After the presentation of the history and the results of the physical examination you'll be asked for the propositions of laboratory tests which might be useful in solving the given clinical problem. The lab test results, differential diagnosis and diagnostic algorithms are all than carefully discussed.

After each two exercises with a given teacher there is a short test to be taken. The aim of the test is the repetition and the assessment of the previously got knowledge. As the test questions are formulated on the principles referring to the USMLE, it is an integral part of your preparation for the exam. To check the given problem understanding, you'll be asked not only to mark the best answer but also to explain briefly why you have chosen this one. After the test correct answers and emerging problems are discussed.

To get credit you are expected to be present on all the exercises (in the case of one justified absence a clinical case related to the missed exercise must be studied in written).

The course finishes with final exam. At least 50% correct answers is required to pass the test.

With any questions or doubts arising from the rules of the course performance, please call Waldemar Myszka MD (wmyszka@amp.edu.pl, phone + 48 501 492 055), who is assigned to serve you with any help.

Prof. Lech Torliński MD, PhD

Department of Laboratory Medicine
Schedule for GROUP A (20.11.2006 – 15.12.2006)

Group	20th of Nov	21st of Nov	22nd of Nov	23rd of Nov	24th of Nov	27th of Nov	28th of Nov	29th of Nov	30th of Nov	1st of Dec	4th of Dec	5th of Dec	6th of Dec	7th of Dec	8th of Dec	11th of Dec	12th of Dec	13th of Dec	14th of Dec	15th of Dec
6	V	VI	III		IV	I	II		VII	VIII	IX	X			XIII	XI	XII			FINAL EXAM
7	VII	VIII				IX	X	I	II		XI	XII	V	III	IV	VI	XIII			
8	XII	XI	V		VII	VIII		III	VI	IV	I	II	IX		X	XIII				
9	IX	X	XI		XII		VII	VIII		XIII	V	VI	I	II		III	IV			
10	I	II	IX		X		XI	XII		V	III	IV	XIII		VI	VII	VIII			

XX - classes - day off

6	7	8	9	10
Dreisbach, Jeremiah	Walker, Travis	Rahman, Sakibur	Ashkar, Jameel	Rakoczy, Katherine
Chen , I-Cheng	Trelease, Shannon	Khabbaz, Omar	Chomicz, Grzegorz	Barnett, Robert
Weerdenburg, Kirsten	Vandervelde, Gerry	Ketema, Mulugeta	Werpachowski, Jack	Dilmaghani-Tabriz, Darah
Yamani, Feisal	Salejee, Ismail	Saleh, Fahad	Plumptre, Adewale	
	Badger, Christopher	Latefi, Babak	Ogun, Oluwatobi	

You'll be looked forward at the following places...

	EXERCISE		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
GROUP A	6	Date	**27.11**	**28.11**	**22.11**	**24.11**	**20.11**	**21.11**	**30.11**	**1.12**	**4.12**	**5.12**	**11.12**	**12.12**	**8.12**
		Place	Dąbrowskiego room 903	Dąbrowskiego room 905	Dąbrowskiego room 905	Dąbrowskiego room 905	Dąbrowskiego room 905	Dąbrowskiego room 905	Collegium Chemicum	Dąbrowskiego room 912	Dąbrowskiego room 608	Dąbrowskiego room 608	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 912
	7	Date	**29.11**	**30.11**	**7.12**	**8.12**	**6.12**	**11.12**	**20.11**	**21.11**	**27.11**	**28.11**	**4.12**	**5.12**	**12.12**
		Place	Dąbrowskiego room 912	Dąbrowskiego room 608	Dąbrowskiego room 412	Dąbrowskiego room 905	Dąbrowskiego room 905	Dąbrowskiego room 903	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 608	Dąbrowskiego room 608	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 912
	8	Date	**4.12**	**5.12**	**29.11**	**1.12**	**22.11**	**30.11**	**24.11**	**27.11**	**6.12**	**8.12**	**21.11**	**20.11**	**11.12**
		Place	Dąbrowskiego room 903	Dąbrowskiego room 412	Dąbrowskiego room 905	Dąbrowskiego room 905	Dąbrowskiego room 912	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 905	Dąbrowskiego room 608	Dąbrowskiego room 608	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 912
	9	Date	**6.12**	**7.12**	**11.12**	**12.12**	**4.12**	**5.12**	**28.11**	**29.11**	**20.11**	**21.11**	**22.11**	**24.11**	**1.12**
		Place	Dąbrowskiego room 912	Dąbrowskiego room 608	Dąbrowskiego room 905	Dąbrowskiego room 905	Dąbrowskiego room 912	Dąbrowskiego room 912	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 608	Dąbrowskiego room 608	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 608
	10	Date	**20.11**	**21.11**	**4.12**	**5.12**	**1.12**	**8.12**	**11.12**	**12.12**	**22.11**	**24.11**	**28.11**	**29.11**	**6.12**
		Place	Dąbrowskiego room 903	Dąbrowskiego room 912	Dąbrowskiego room 905	Dąbrowskiego room 905	Dąbrowskiego room 903	Dąbrowskiego room 903	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 608	Dąbrowskiego room 608	Collegium Chemicum	Collegium Chemicum	Dąbrowskiego room 411

Collegium Chemicum, Grunwaldzka 6, Department of Chemistry and Clinical Biochemistry, 2nd floor (via the passage through the students' reading-room)

Dąbrowskiego, Collegium Adama Wrzoska, Dąbrowskiego 79

No. of exercise	List of topics/leading teachers' names/Contents		
I	**The usefulness of laboratory data in the differential diagnosis of anemia/** Wojciech Żak MD	4 hrs	4.00 – 7.00 p.m.
II	**Basic laboratory tests in the diagnosis and management of haemostatic failure/** Wojciech Żak MD	5 hrs	4.00 – 7.45 p.m.
III	**The evaluation of acid-base balance in clinical practice/** Waldemar Myszka MD	4 hrs	4.00 – 7.00 p.m.
IV	**Diagnostic approach to water-electrolyte disturbances/** Waldemar Myszka MD	5 hrs	4.00 – 7.45 p.m.
V	**Biochemical effects of neoplastic diseases/** Miłosława Zowczak-Drabarczyk MD	4 hrs	4.00 – 7.00 p.m.
VI	**Plasma proteins.** **Laboratory diagnosis of inflammation and infectious diseases /** Miłosława Zowczak-Drabarczyk MD	5 hrs	4.00 – 7.45 p.m.
VII	**Urinalysis and other laboratory procedures in the diagnosis of urinary tract disorders/** Dorota Formanowicz MD	3 hrs	4.00 – 6.15 p.m.
VIII	**Acute and chronic kidney failure.** **Clinical basics of haemodialysis/** Dorota Formanowicz MD	3 hrs	4.00 – 6.15 p.m.
IX	**The application of laboratory methods in the diagnosis and management of heart diseases/** Hanna Kara-Perz MD	4 hrs	4.00 – 7.00 p.m.
X	**Clinical enzymology and liver function disorders/** Hanna Kara-Perz MD	5 hrs	4.00 – 7.45 p.m.
XI	**The differential diagnosis of lipid metabolism disorders.** /Ewa Wysocka MD / Prof. Lech Torliński MD, PhD (Laboratory tests)	4 hrs (3 hrs)	4.00 – 7.00 p.m.
XII	**Laboratory tests in the diagnosis of hyper- and hypoglycemia** / Ewa Wysocka MD / Prof. Lech Torliński MD, PhD (Laboratory tests)	5 hrs (3 hrs)	4.00 – 7.45 p.m.
XIII	**Age-dependent characteristics of laboratory tests/** Sylwia Dzięgielewska MD	3 hrs	4.00 – 6.15 p. m.

S Y L L A B U S

EXERCISE I: **The usefulness of laboratory data in the differential diagnosis of anemia**

TEACHER'S NAME: Wojciech Żak MD

CONTENTS: Exercise - 4 x 45 min. (4.00 – 7.00 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to:*

- order a Complete Blood Count (CBC) correctly
- interpret any abnormal CBC result
- make use of a CBC as the first step in the differential diagnosis of anaemia
- choose effective laboratory tests to determine the cause of anemia

REVISION: *Since cases* of *micro-, normo- and macrocytic anemia will be analysed*, *revision and consideration of the following issues would be beneficial:*

- pathophysiological and morphological classification of anemias (according to MCV)
- general and specific symptoms and signs of anemias

EXERCISE II: **Basic laboratory tests in the diagnosis and management of haemostatic failure**

TEACHER'S NAME: Wojciech Żak MD

CONTENTS: Exercise - 5 x 45 min. (4.00 – 7.45 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to:*

- recognize the clinical conditions, where estimation of hemostasis is particularly indicated
- conduct such an estimation with the help of basic (screening) laboratory tests
- differentiate between primary and secondary hemostasis defect
- formulate a hypothesis concerning the cause of hemostatic failure according to its clinical presentation and the results of the screening lab tests
- decide the most cost-effective selection of further laboratory analyses to determine the differential diagnosis of the commonest hemorrhagic diatheses
- monitor the anticoagulant treatment

REVISION: *Since a case study will form the background to discussing the diagnostic algorithms*, *revision of the following issues would be useful*:

- physiology of hemostasis and the diagnostic significance of basic laboratory tests aiming to its estimation (BT, PT, APTT, TT)
- clinical symptoms and signs of the hemorrhagic diatheses
- causes of thrombocytopenia

EXERCISE III: The evaluation of acid-base balance in clinical practice

TEACHER'S NAME: Waldemar Myszka MD

CONTENTS: Exercise – 4 x 45 min. (4.00 – 7.00 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to:*

- properly evaluate results of blood gases analysis
- differentiate between simple and mixed acid-base balance disorders on the base of clinical and laboratory data
- monitor treatment of acid-base balance disorders

REVISION: *Clinical cases of patients with metabolic and respiratory acidosis and alkalosis will be considered, so revision of the following problems is advisable:*

- the chemical and physiologic bases of:
  - hydrogen ion concentration (pH), buffering, carbonic acid – bicarbonate buffer system, Henderson-Hasselbalch equation, anion gap, osmotic gap,
    - renal contribution to hydrogen ion balance: bicarbonate reabsorption, acid excretion, titratable acidity,
    - carbon dioxide excretion
- normal values of laboratory acid-base balance indicators:
  - pH, pCO_2, pO_2, HCO_3^-, BE, O_2 sat.

EXERCISE IV: Diagnostic approach to water – electrolyte disturbances

TEACHER'S NAME: Waldemar Myszka MD

CONTENTS: Exercise - 5 x 45 min. (4.00 – 7.45 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to:*

- obtain useful data from the clinical history and physical examination followed by properly selected laboratory tests
- interpret abnormal results of plasma electrolyte concentration in particular clinical situations
- properly replace water and electrolyte loses
- choose laboratory tests for monitoring treatment of water-electrolyte disorders

REVISION: *As the clinical cases of patients presenting with dehydration, overhydration (oedema), hypo- and hypernatremia and hypo- and hyperkaliemia will be discussed, one should review the following issues*:

- definition of terms: osmolality, effective osmolality, isotonic, hypertonic, and hypotonic solutions, hydrostatic pressure, osmotic pressure, oncotic pressure
- water-sodium balance
- potassium balance

EXERCISE V: Biochemical effects of neoplastic diseases

TEACHER'S NAME: Miłosława Zowczak-Drabarczyk MD

CONTENTS: Exercise - 5 x 45 min. (4.00 – 7.45 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to*:

- suspect a neoplastic process when observing various abnormalities in basic lab parameters
- make use of tumor markers in the diagnosis and management of neoplastic disease

REVISION: *As we shall be studying a number of clinical cases prepare, please, short revision on the following tumor markers:*

- CEA
- AFP
- PSA
- CA 125
- CA 19-9
- CA 15-3
- beta-hCG

EXERCISE VI: Plasma proteins and laboratory diagnosis of inflammation and infectious diseases

TEACHER'S NAME: Miłosława Zowczak-Drabarczyk MD

CONTENTS: Exercise - 4 x 45 min. (4.00 – 7.00 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to*:

- order suitable lab tests and interpret their results when
  - observing clinical manifestations of disorders resulting in serum and/or urine proteins abnormalities
  - suspecting inflammatory process of either infective (bacterial, viral) or non infective etiology

REVISION: *To work on an actual case study, please revise the following*:

- hypo- and hyperproteinemias
- proteinuria
- interpretation of serum protein electrophoresis abnormalities
- lab tests for identification of monoclonal protein
- lab tests for identification of specific proteins
- innate and adaptive immunity components and mechanisms
- inflammatory process and its mediators
- complement components-useful analysis
- cytokines-useful analysis
- positive and negative acute phase proteins
- interpretation of ESR changes
- CBC changes due to infection/inflammation
- interpretation of increased CRP concentration in various inflammatory conditions
- lab tests for differentiation between infective and non infective inflammation, and between bacterial and viral ones.

EXERCISE VII: Urinalysis and other laboratory procedures in the diseases of urinary tract

TEACHER'S NAME: Dorota Formanowicz MD

CONTENTS: Exercise - 3 x 45 min. (4.00 – 6.15 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to:*

- interpret the results of urine and blood analyses used in the assessment of renal function and the diagnosis of selected diseases of the urinary system

REVISION: *For this exercise revision of the following issues would be useful:*

- glomerular filtration rate
- regulation of water- electrolyte and acid-base balance
- mechanisms of urine concentration and dilution

Attention please! Before this exercise (in the morning after minimally 8 hrs fasting) you are asked to deliver your urine samples to the laboratory (Collegium Chemicum, Grunwaldzka 6).During the first part of this exercise urinalysis (urine: pH, specific gravity, glucose, bilirubin, ketones, protein (microalbuminuria), nitrate, blood and leukocytes) of your urine samples will be performed.
Please take white coats.

EXERCISE VIII: Kidney failure and clinical basics of dialysis

TEACHER'S NAME: Dorota Formanowicz MD

CONTENTS: Exercise - 3 x 45 min. (4.00 – 6.15 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to:*

- differentiate between prerenal, renal and postrenal acute renal failure
- differentiate between acute renal failure and chronic kidney disease
- monitor progression of chronic kidney disease
- choose laboratory tests for monitoring state of uremic patient and interpret abnormal results of selected laboratory tests of blood and urine
- list indications and contraindications for dialysis treatment

REVISION: *For this exercise revision of the following issues would be useful:*

- glomerular filtration rate
- regulation of water-electrolyte and acid-base balance
- mechanisms of urine concentration and dilution
- regulation of calcium-phosphate balance

EXERCISE IX: The application of laboratory methods in the diagnosis and management of ischemic heart disease

TEACHER'S NAME: Hanna Kara-Perz MD

CONTENTS: Exercise - 4 x 45 min. (4.00 – 7.00 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to:*

- select and interpret the laboratory tests indicated in a patient with suspected myocardial infarction
- make a total assessment of the risk factors of ischemic heart disease

REVISION: *Recollection of information concerning the following issues would be beneficial*:

- myocardial oxygen demand and supply
- clinical manifestations of myocardial ischemia

EXERCISE X:Clinical enzymology and liver function disorders diagnosis

TEACHER'S NAME: Hanna Kara-Perz MD

CONTENTS: Exercise - 5 x 45 min. (4.00 – 7.45 p.m.)

OBJECTIVE: A*fter completion of this exercise you should be able to*:

- order lab tests reasonably and interpret their results when:
  - suspecting liver disorder

REVISION: *To work on an actual case study, please revise the following*:

- serum conjugated and unconjugated bilirubin
- bilirubin and urobilinogen in urine
- alkaline phosphatase (ALP)
- lactic dehydrogenase (LDH)
- gamma GT (GGTP)
- prothrombin time (PT)
- serum protein profile
- acute phase proteins
- blood ammonia

EXERCISE XI: The differential diagnosis of disorders of lipid metabolism

TEACHERS' NAMES: Ewa Wysocka MD/ Prof. Lech Torliński MD, PhD

CONTENTS: Exercise - 5 x 45 min. (4.00-7.45 p.m.)
Laboratory – 2 x 45 min.

OBJECTIVE: *After completion of this exercise you should be able to:*

- diagnose primary and secondary hyperlipoproteinemia
- order the correct biochemical tests for the primary and secondary prevention of Ischemic Heart Disease (IHD)
- assess the lipid risk factors for IHD

REPETITION: *For the clinical diagnosis and laboratory monitoring of hyperlipoproteinemia in the prevention of IHD, please revise:*

- the structure and function of lipoproteins,
- lipoprotein metabolism,
- the pathogenesis of atherosclerosis,
- the risk factors for the development of IHD.

Attention please! During this exercise concentrations of some lipid parameters (triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol) in your blood will be determined and your risk of coronary artery disease according to Framingham system will be calculated.
Please take white coats.

EXERCISE XII: Laboratory tests in the diagnosis of hyper- and hypoglycemia

TEACHERS' NAMES: Ewa Wysocka MD/ Prof. Lech Torliński MD, PhD

CONTENTS: Exercise - 5 x 45 min. (4.00-7.45 p.m.)
Laboratory – 4 x 45 min.

OBJECTIVE: *After completion of this exercise you should be able to:*

- recognize the risk factors for the development of diabetes mellitus (especially type 2)
- diagnose diabetic and prediabetic states
- monitor diabetes mellitus biochemically
- recognize acute and late diabetic complications
- diagnose hypoglycemia

REVISION: *To achieve the aim of this exercise, please revise:*

- carbohydrates' metabolism and its hormonal regulation,
- pathobiochemistry of diabetes mellitus and its complications (acute, late: macro- and microangiopathy),
- the insulin resistance syndrome – syndrome X,
- classification of hyperglycemic states,
- categories of hypoglycemia.

Attention please! During the first part of this exercise you will have an opportunity to estimate your own blood glucose concentration.
Please take white coats.

EXERCISE XIII: Age-dependent characteristics of laboratory tests

TEACHER'S NAME: Sylwia Dzięgielewska MD

CONTENTS: Exercise - 3 x 45 min. (4.00 – 6.15 p.m.)

OBJECTIVE: *After completion of this exercise you should be able to:*

- indicate how biochemical and physiological consequences of ageing are reflected in lab tests,
- differentiate between age-dependent "abnormal" tests results and those which may actually indicate the disease,
- select the most effective tests in the differential diagnosis of symptoms and signs: are they age- or disease-related?
- choose lab tests which are particularly useful in screening and monitoring age-related diseases,
- use laboratory tests in the determination of 6 month or less medical prognosis.

REVISION: *Since a number of clinical cases will be analyzed, please revise:*

- biochemical and physiological changes of ageing

FINAL EXAM

Attention please!
You will be not allowed to take the exam
without your credit books and examination cards.

PART II
Review of Laboratory Medicine

Clinical laboratory tests – reference range

– Prof. Lech Torliński MD, PhD

HEMATOLOGIC	Conventional Units	SI Units
Erythrocyte count (RBC):		
Male:	4.5-6.0 million/mm^3	4.5-6.0x10^{12}/L
Female:	4.0-5.5 million/mm^3	4.0-5.5x10^{12}/L
Erythrocyte sedimentation rate (ESR):		
Male:	0-15 mm/h	
Female:	0-20 mm/h	
Hematocrit (HCT, PCV, Packed Cell Volume):		
Male:	40-54 %	0.40-0.54 L/L
Female:	37-47 %	0.37-0.47 L/L
Hemoglobin A_{1C}	_< 6 %	
Hemoglobin, blood (HGB, HB):		
Male:	13.5-17.5 g/dL,	8.38-10.86 mmol(HbFe)/L
Female:	12-16 g/dL	7.45-9.93 mmol(HbFe)/L
Hemoglobin, plasma:	1-4 mg/dL	
Haptoglobin:	100-250 mg/dL	
Leukocyte count (WBC):	4-10 thousand/mm^3	4.0-10.0x10^9/L
Leukocyte-differential:		
band neutrophils (Bands)	3-5 %	0.03-0.05
segmented neutrophils (Segs)	40-65 %	0.40-0.65
monocytes (Mono)	3-7 %	0.03-0.07
eosinophils (Eosi)	1-3 %	0.01-0.03
basophils (Baso)	0-1 %	0.00-0.01
lymphocytes (Lymph)	20-45 %	0.20-0.45
Mean corpuscular hemoglobin (MCH):	27-32 pg/cell	
Mean corp.hemogl.concentration (MCHC):	31-36 g/dL	
Mean corpuscular volume (MCV):	80-100 fL	
RBC volume distribution width (RDW):	11.5-14.5 %	
Platelet count (PLT):	140-400 thousand/mm^3	140-400 x 10^9/L

Reticulocyte count:

Relative reticulocyte count (RET): 0.5-2.0 % RBC

Absolute reticulocyte count (ARC): 25-75 x 10^9/L

Corrected reticulocyte count (CRC): < 2 %

CRC% = RET% (anemia) x [HCT%(anemia) / HCT 45%]

Reticulocyte production index (RPI): > 3

RPI = CRC% / maturationtime

Lymphocyte (diff): B cell …… 1-25 %
Total T, CD3 …… 60-87 %
Helper, CD4 …… 30-55 %
Suppr, CD8 ……. 10-40 %
H : S, CD4/CD8 …….. 0.8-3.0

Bleeding time (BT): 2 – 7 min

Partial thromboplastin time activated (APTT): 25-40 sec

Prothrombin time (PT): 11-15 sec

INR 0.9-1.1

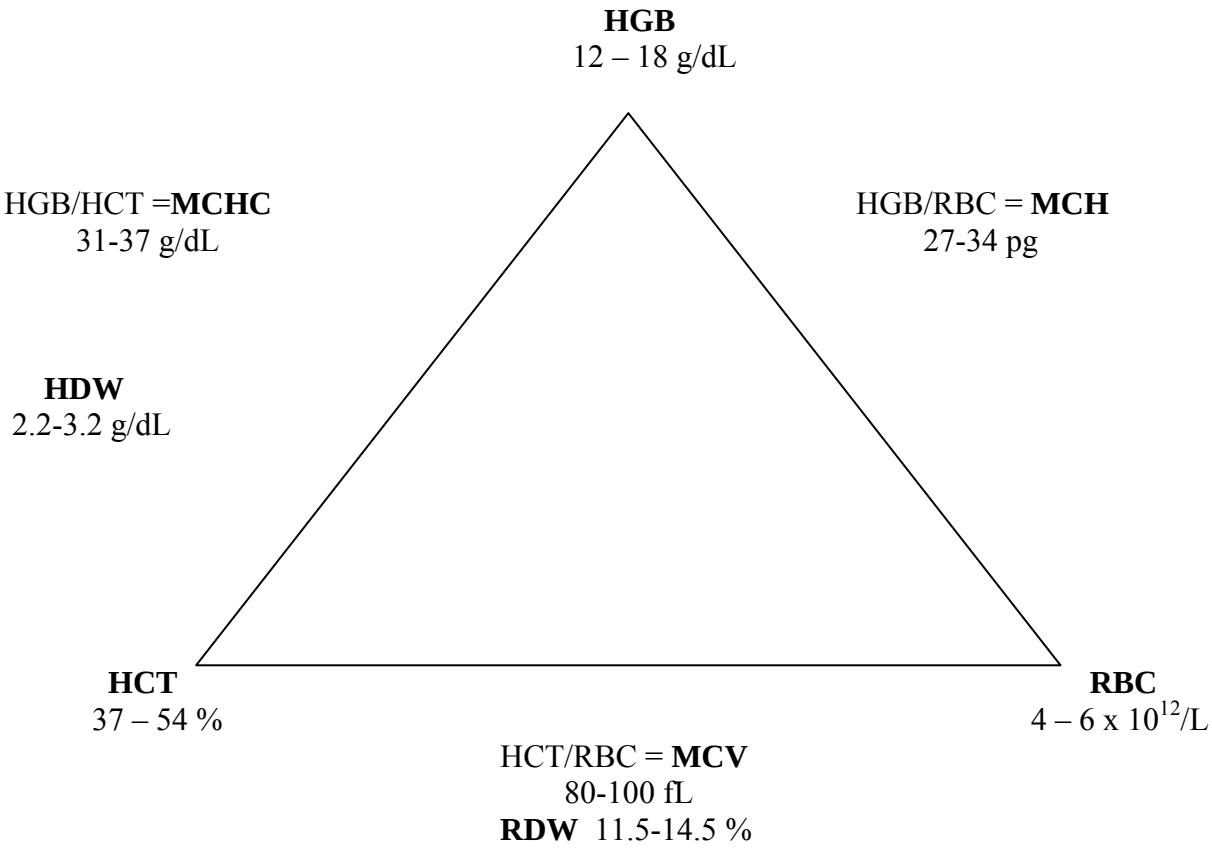
Thrombin time (TT): 10-14 sec

Fibrinogen: 200-400 mg/dL

Beta-2 microglobulin: < 2.0 mg/L

Volume plasma: Male: 25-43 mL/kg, Female: 28-45 mL/kg

Volume red cell: Male: 20-36 mL/kg, Female: 19-31 ml/kg



RBC x 3 = HGB

HGB x 3 = HCT

HCT : 9 = RBC

HYPERCHOLESTEROLEMIA

Cholesterol mg/dL x 0.0259 = mmol/L

Total Chol. > 190 mg/dL	> 4.93 mmol/L
LDL Chol. >115 mg/dL	> 2.98 mmol/L
TG < 200 mg/dL	< 2.28 mmol/L

HLP phenotypes:

type II a :	high Cholesterol	high LDL
type VI :	high Cholesterol	high HDL

HYPERTRIGLYCERIDEMIA

Triglycerides (TG) mg/dL x 0.0114 = mmol/L

TG > 200 mg/dL	> 2.28 mmol/L
Total Chol. < 190 mg/dL	< 4.93 mmol/L
LDL Chol. < 115 mg/dL	< 2.98 mmol/L

HLP phenotypes:

type I :	high TG	high Chylomicrons
type IV :	high TG	high VLDL
type V :	high TG	high Chylomicrons and high VLDL

THE FRIEDEWALD FORMULA

LDL Chol = T.Chol – HDL Chol – TG/5

MIXED HYPERLIPOPROTEINEMIA

Total Chol. > 190 mg/dL	> 4.93 mmol/L
LDL Chol.> 115 mg/dL	> 2.98 mmol/L
TG > 200 mg/dL	> 2.28 mmol/L

HLP phenotypes:

type IIb :	high Cholesterol and high TG	high LDL and high VLDL
type III :	high Chol. and high TG	high VLDL with beta mobility

HIGH RISK OF CVD

TG > 200 mg/dL
T.Chol > 190 mg/dL
LDL Chol > 115 mg/dL
HDL Chol < 35 mg/dL
T.Chol / HDL Chol > 3
[HDL+ VLDL+ LDL] / HDL > 3
Lp(a) > 30 mg/dL
Apolipoprotein A < 2.43 g/L
Apolipoprotein AI < 1.15 g/L
Apolipoprotein B_{100} > 1.6 g/L Male
> 1.5 g/L Female
Homocysteine > 16 μmol/L

BIOCHEMICAL MARKERS OF AMI

MARKER	TIME OF FIRST INCREASE	PEAK	DURATION OF INCREASE
Myoglobin	1-3 h	~6h	12-24 h
CK-MB mass	3-4 h	~14h	24-46 h
cTn T	3-4 h	~18 h	10-14 days
cTn I	4-6 h	~19 h	4-7 days

NORMAL FASTING PLASMA GLUCOSE

60-110 mg/dL 3.33-6.10 mmol/L

NORMAL PLASMA GLUCOSE

2 hours after OGTT < 140 mg/dL

NORMAL BLOOD GAS VALUES

pH	arterial …….	7.37 – 7.43
	capillary ……..	7.36 – 7.42
	venous ……..	7.32 – 7.38
pCO_2	arterial …….	36 – 44 mm Hg
	capillary ……..	35 – 45 mm Hg
	venous ……..	42 – 50 mmHg
pO_2	arterial …….	74 – 108 mm Hg
	capillary ……..	65 – 95 mmHg
	venous ……..	~ 40 mm Hg
$SatO_2$	arterial …….	92 – 96 %
	capillary ……..	70 – 95 %
	venous ……..	54 – 69 %
$[HCO_3^-]$	arterial …….	22 – 26 mmol/L
	capillary ……..	21 – 27 mmol/L
	venous ……..	23 – 27 mmol/L

Normal range of base excess in arterial -2.5 to +2.5 mmol/L
Negative base excess -BE < -2.5 mmol/L
Positive base excess +BE > +2.5 mmol/L

ACIDOSIS AND ALKALOSIS

	pH	BE mmol/L	PCO_2 mm Hg	corrected $[HCO_3^-]$ mmol/L
respiratory ACIDOSIS	< 7.36	> +2.5	> 45	> 24
uncompensated	low		high	
compensation				high
metabolic ACIDOSIS	< 7.36	< -2.5	< 35	< 24
uncompensated	low			low
compensation			low	
respiratory ALKALOSIS	> 7.42	< -2.5	< 35	< 24
uncompensated	high		low	
compensation				low
metabolic ALKALOSIS	> 7.42	> +2.5	> 45	> 24
uncompensated	high			high
compensation			high	

BODY WATER

Total body water: M. ~60% of body mass
F. ~50% of body mass
Proportion of total body water: intracellular, two thirds
extracellular, one thirds
Normal osmolality 275-295 mOsm/kg H_20
Anion gap 8-16 mmol/L $AG = [Na^+] - \{[HCO_3^-] + [Cl^-]\}$
Corrected $[HCO_3^-]$ = measured $[HCO_3^-]$ + (anion gap – 12)

ANIONS IN SERUM

Chloride (Cl^-) 102 mEq/L, 102 mmol/L, 96-106 mmol/L

Bicarbonate (HCO_3^-) 26 mEq/L, 26 mmol/L, 24-28 mmol/L

Proteins 15 mEq/L,70 g/L

Organic acids 5 mEq/L

Phosphates (HPO_4^{2-}) 2 mEq/L, 1 mmol/L, 2.5-5.0 mg/dL

Symptoms of hypophosphatemia (phosphate < 2.5 mg/dL) :
weakness, lethargy, irritability, depressed cardiac and respiratory function, hypotension, cardiac arrhythmias, red and white cell dysfunction, skeletal demineralization
Symptoms of hyperphosphatemia (phosphate > 5 mg/dL):
pruritas; otherwise, symptoms are unremarkable

Sulphates (SO_4^{2-}) 1 mEq/L, 0.5 mmol/L

CATIONS IN SERUM

Sodium (Na^+) 142 mEq/L, 135-145 mEq/L, 142 mmol/L

Symptoms of hyponatremia (sodium < 135 mEq/L):
confusion, lethargy, stępor, coma, nausea, vomiting, headache, irritability,muscle twitches, seizures (usually when hyponatremia develops rapidly)
Symptoms of hypernatremia (sodium > 145 mEq/L):
lethargy, confusion, restlessness, seizures, coma, hyperreflexia, spasticity (neurologic symptoms are due to dehydration of brain cells)

Potassium (K^+) 5 mEq/L, 3.5-5 mEq/L, 5 mmol/L

Symptoms of hypokalemia (potassium < 3.5 mEq/L):
neuromuscular (muscle weakness, paralysis, rhabdomyolysis, hyporeflexia), gastrointestinal (paralytic ileus), renal (polyuria, polydipsia, secondary decreased concentrating ability), cardiac (ECG findings include T-wave flattening and inversion, U-wave and ST segment depression.Hypokalemia enhances cardiac toxicity of digitalis)
Symptoms of hyperkalemia (potassium > 5 mEq/L):
weakness, parasthesias, flaccid paralysis,ventricular fibrillation, cardiac arrest

Calcium (Ca) 5 mEq/L, 2.5 mmol/L, 8.5-10.5 mg/dL
Calcium ionized (Ca^{2+}): 1.05-1.30 mmol/L

Symptoms of hypocalcemia (calcium < 8.5 mg/dL):
cardiovascular (hypotension, bradycardia, asystole, impaired contractility, QT prolongation and T-wave inversion on ECG, digitalis insensitivity), respiratory (bronchospasm and laryngeal spasm), neuromuscular (weakness, paresthesias, tetany, muscle spasm, Chvostek`s and Trousseau`s signs, hyperreflexia and seizures), psychiatric (anxiety, depression, irritability, confusion, dementia and psychosis)
Symptoms of hypercalcemia (calcium > 10.5 mg/dL):
also known as "stones, bones, groans and psychiatric overtones, cardiovascular (hypertension, bradycardia, first-degree AV block, increased repolarization,shortened QT interval), gastrointestinal (constipation, anorexia, nausea and vomiting, peptic ulcer disease, pancreatitis), renal (polyuria and polydipsia, nocturia, renal insufficiency, nephrolithiasis), musculoskeletal (weakness, myopathy, osteoporosis, bone pain), neurologic (decreased concentration, depression, confusion, psychosis,coma), other (pruritus, metastatic calcification)

Magnesium (Mg^{2+}) 2 mEq/L, 1 mmol/L 1.8-2.3 mg/dL

Symptoms of hypomagnesemia (magnesium < 1.8 mg/dL):
cardiovascular (arrhythmias, e.g. atrial fibrillation and torsades de pointes,prolonged PR and QT intervals, T-wave flattening), neuromuscular (weakness, seizures, delirium, coma, hyperreflexia, fasciculations, Chvostek`s and Trousseau`s signs)
Symptoms of hypermagnesemia (magnesium > 2.3 mg/dL):
respiratory (respiratory depression, apnea), cardiovascular (hypotension, cardiac arrest, ECG findings : prolonged QRS complexes and QT intervals, heart block, peaked T waves), gastrointestinal (nausea and vomiting), neuromuscular (paresthesias, somnolence, confusion, coma, hypereflexia, paralysis, apnea)

CLICAL CHEMISTRY, serum

BUN	8 - 25 mg/dL	
Creatinine	0.5 - 1.5 mg/dL	
Glucose	60 - 110 mg/dL	3.33 - 6.10
Uric acid	2.4 - 7.5 mg/dL	mmol/L
Total protein	6 - 8 g/dL	
Albumin	3.4 - 5.4 g/dL	
Globulin	2.3 – 3.5 g/dL	
Total bilirubin	0.2 - 1.5 mg/dL	
Direct bilirubin	0.0 – 0.3 mg/dL	3.4 - 25.5 µmol/L
GOT, AST	0 - 40 U/L	
GPT, ALT	0 – 40 U/L	
GGTP	10 – 50 U/L	
LDH	50 – 240 U/L	
CK	5 – 200 U/Dl	
Iron	50 – 160 µg/Dl	
TIBC	240 – 425 µg/dL	
Iron % Sat	20 – 55 %	
Ferritin	30 – 250 ng/mL	30 – 250 mg/L

URINE EXAMINATION

MICROALBUMINURIA	30 - 300 mg/day
ALBUMINURIA	> 300 mg/day
PROTEINURIA	1 – 3 g/day
Creatinine	0.75-1.5 g/day
Albumin : creatinine (A : C)	30-300 mg alb/g crea

The usefulness of laboratory data in the differential diagnosis of anemia

Wojciech Żak MD

If one suspects a pathology affecting the hematopoietic system

↓

CBC

(Complete Blood Counting)

is the laboratory procedure of choice in the 1st step of the diagnostic process
since it makes possible an evaluation of 3 basic corpuscular components of the blood:

red blood cells
white blood cells
platelets

Anemia seems to be the most common hematological problem to confront any branch of medicine.
It usually develops as a chronic, discrete process and the abnormalities in laboratory data often precede the clinical picture.

ABNORMALITIES IN LABORATORY DATA → CLINICAL PICTURE OF ANEMIA

BIOCHEMICAL ASSAYS CBC

Therefore anemia should be suspected and CBC performed

not only in patients already presenting with its clinical symptoms or signs

but

also in patients with increased risk of anemia's evolution,
(although they have not presented yet the clinical picture of anemia)
related to:

1. **clinical state or disease of possible direct influence on the red cell system**
(e.g. pregnancy, inflammation, renal insufficiency, hypothyroidism)
2. **a disease which requires taking drugs of such an influence**
(without a direct affect on the hematopoietic system of the disease per se, e.g. epilepsy)

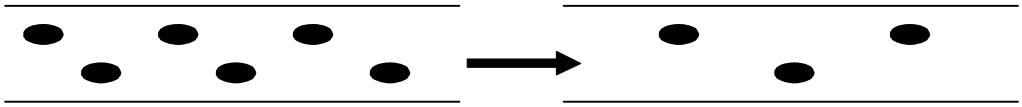
The significance of CBC as a starting-point in the diagnostic process of anemia

1. **To confirm (or verify) the clinical hypothesis of anemia**
2. **To carry out the first steps of the differential diagnosis**

(to select the most effective farther laboratory procedures to find its cause)

ANEMIA

=
a significant reduction in the red cell mass
and
a corresponding decrease in the oxygen carrying capacity of the blood.



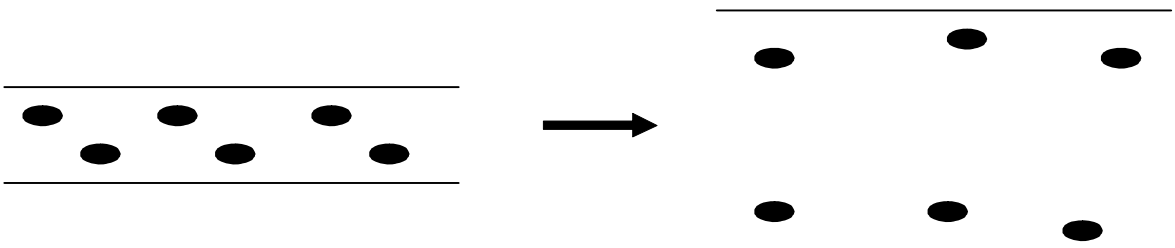
Since normally blood volume is maintained at a nearly constant level
it entails a **decrease** of some peripheral blood values,
(components of the CBC):

RBC (red blood cell count / unit of the whole blood volume)
HGB (mass of hemoglobin / unit of the whole blood volume)
= hemoglobin concentration)
HCT (volume of the red cells / unit of the whole blood volume)

BUT

RBC
HGB
HCT

- not always reflects a real reduction
in the red cell mass
(anemia)
- it also happens only due to an expanded blood volume
('pseudoanemia', e. g. pregnancy, congestive heart failure)



On the other hand

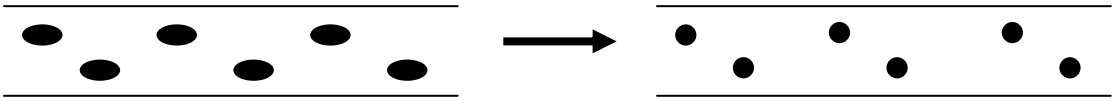
- **a real anemia not necessarily presents**

with a simultaneous decrease of all these values (RBC, HGB, HCT)

particularly at the early stages of its development

e.g. iron deficiency
(disturbed hemoglobin synthesis makes red cells smaller,
but – at least at the beggining – without a significant affect on their number)

iron defficiency (early stage)



RBC N

HGB ↓

HCT ↓

CONCLUSION

To diagnose an anemia one must:

1. **find a significant decrease of at least 2 of these 3 basic red cell system values in the CBC (RBC, HGB, HCT)**
(below the lower normal limit for patient's age and sex)

2. **exclude an expanded blood volume as a cause of such a decrease**
(particularly if it is mild an the only abnormality in the CBC)

Major components of the CBC

(obtained by electronic hematological counters)

+

and average ranges of reference (normal) values for adults

Parameter(s) ***reflecting status of the red blood cell system***

	Units	***Females***	***Common***	***Males***
RBC	(x 10^{12}/L or T/L)	**4,0 - 5,5**		**4,5 - 6,0**
HGB	g/dL	**12 - 16**		**14 - 18**
HCT	(L/L or %)	**0,37 – 0,47**		**0,40 – 0,54**
MCV (Mean Corpuscular Volume)	fL (x 10^{-15} L)		**80 - 100**	
RDW (Red blood cell Distribution Width)	(%)		**11,5 - 14,5 (<15)**	
MCH (Mean Corpuscular Hemoglobin)	pg (x 10^{-12} g)		**27 - 32**	
MCHC (Mean Corpuscular Hemoglobin Concentration)	g/dL		**32 - 37**	

Reticulocyte Count (absolute - provided only by the newest generation of hematological counters;
- if not and needed -
an additional order is required to get a relative one by the manual method)

- Relative (% - of RBC) **0,5 - 1,5**
- Absolute (x 10^9/L or G/L) **30 - 70**

reflecting status of the white blood cell system

WBC (white blood cell count) (x 10^9/L or G/L) **4,0 - 10**

**Usually hematological counters present also the percentage of some WBC populations;
to evaluate more accurately all of them the peripheral blood smear is required and the references are given below:**

band neutrophils	(% of WBC)	**1 - 5**
segmented neutrophils	(% of WBC)	**40 - 70**
lymphocytes	(% of WBC)	**20 - 45**
monocytes	(% of WBC)	**3 - 8**
eosinophils	(% of WBC)	**1 - 5**
basophils	(% of WBC)	**0 - 1**

reflecting status of the platelets

PLT (platelet count) (x 10^9/L or G/L) **140 - 400**

The remainder platelet parameters (**MPV, PDW, PCT)**
are of less diagnostic significance in everyday clinical practice!

Major steps of analysis of CBC results in the diagnosis of anemia

I.Is the patient really anemic?

↓ *check the basic parameters of the red blood cell system (see: previous pages)*

RBC, HGB, HCT

II. What kind of anemia is it morphologically?

↓ *check the red blood cell indices*

1. **MCV** (micro-, normo-, macrocytic)
2. **RDW** (anisocytic or not)
3. **MCH + MCHC** (hypo-, normo-, hyperchromic)

III. Is the pathology affecting only red blood cell system?

↓ *check the parameters referring to remainder corpuscular elements of the blood*

1. **WBC + % of different WBC populations**
2. **PLT**

IV. Confront the CBC results with the clinical picture

V. Select the most effective laboratory procedures to find the cause of anemia

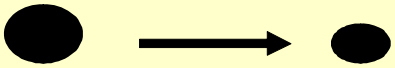
The most important initial step in the differential diagnosis of anemia indicating directions of farther necessary investigations is its morphological classification according to red blood cell indices, with outstanding significance of

MCV

(discussed in details on seminar)

ANEMIA
with
MCV: < 80 fl
↓
microcytic anemia

Since more than 90% of erythrocyte volume is fulfilled with **hemoglobin**
it suggests **a defect in hemoglobin synthesis**



Synthesis of **HEMOGLOGIN** molecule requires:

IRON | **HEME** | **GLOBIN**

and may be disturbed by:

insufficient amount of iron delivered to the bone marrow

impaired heme synthesis
(congenital or acquired enzyme dysfunction)

impaired synthesis of globin chains

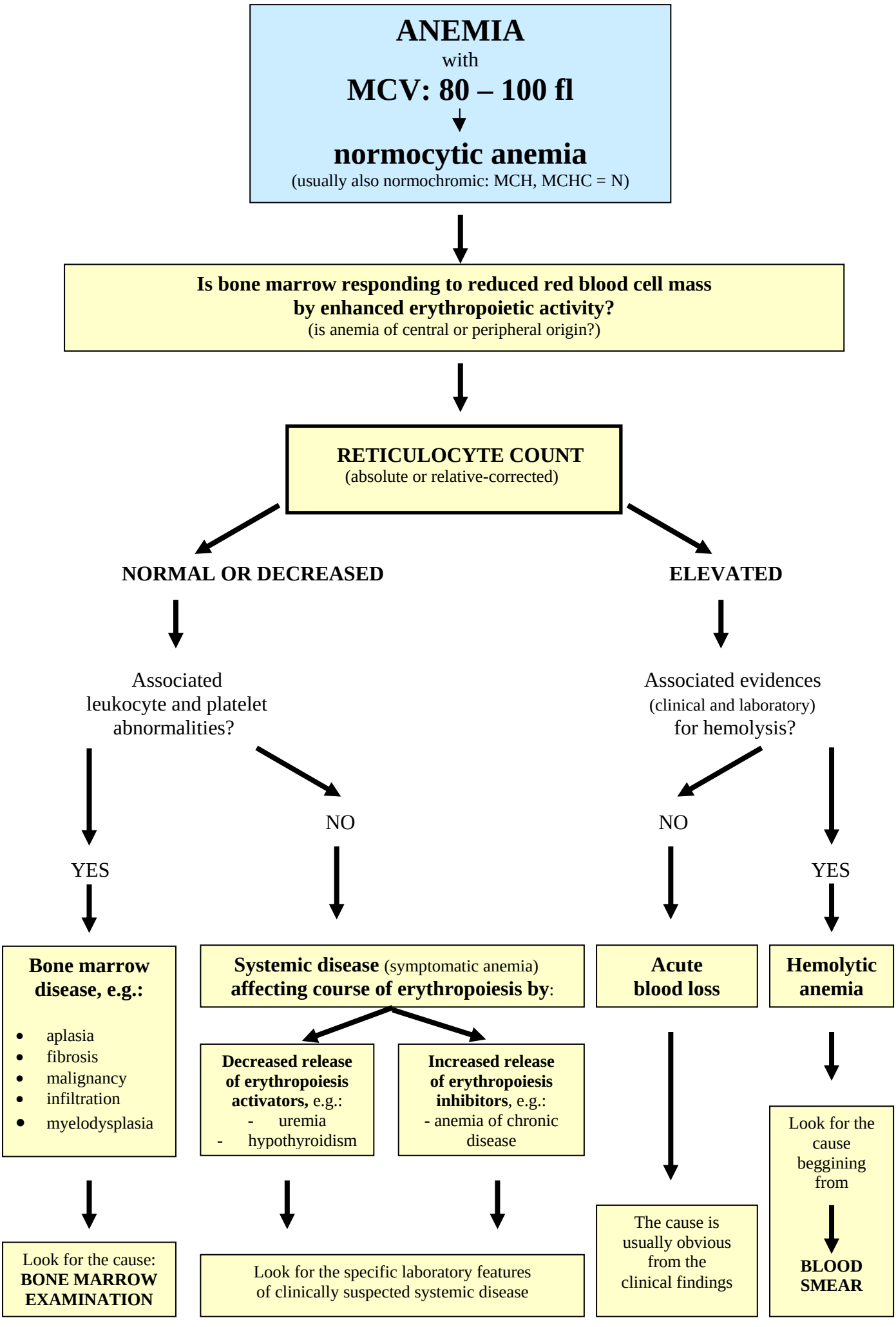
IRON DEFFICIENCY

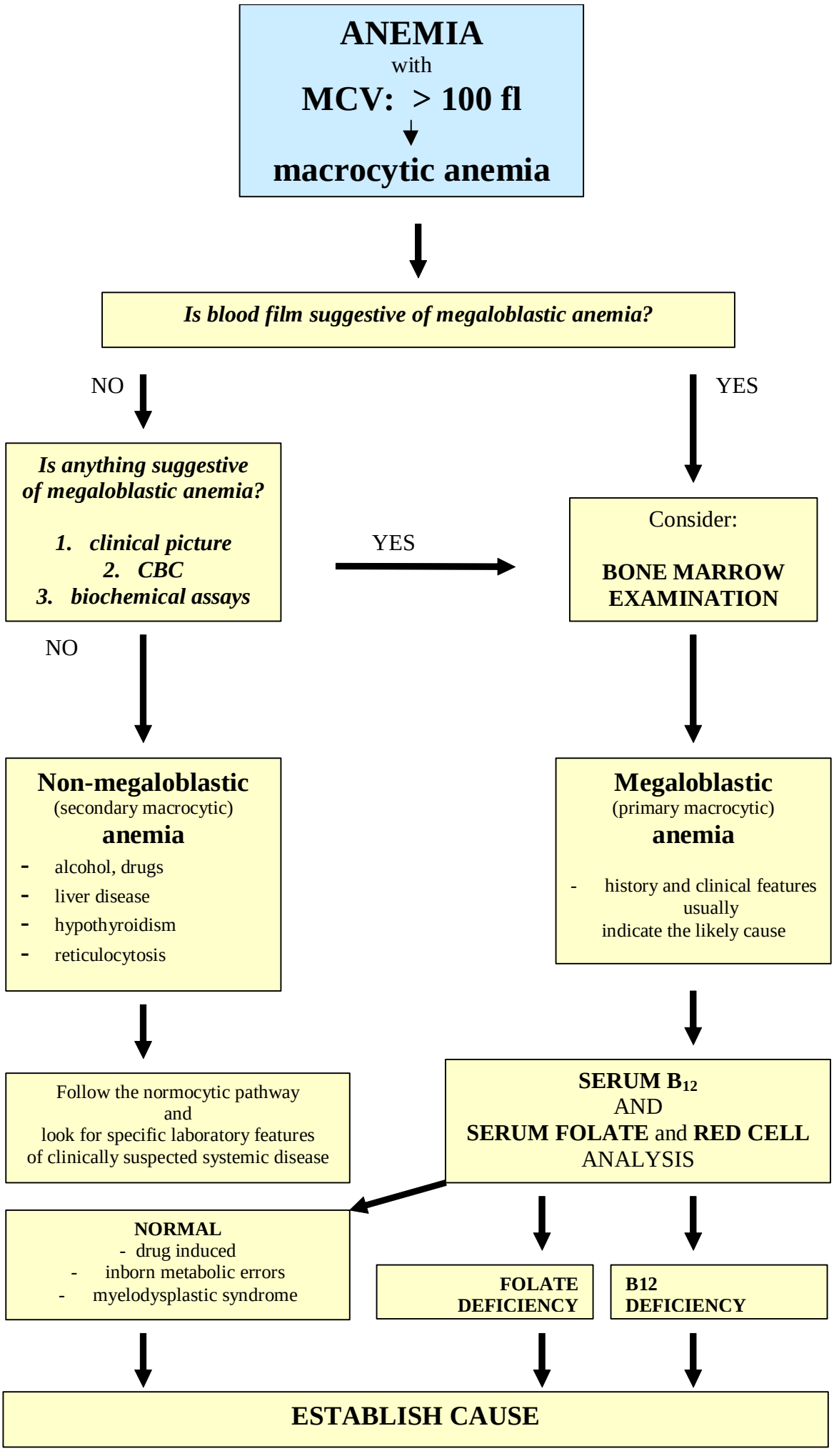
SIDEROBLASTIC ANEMIA

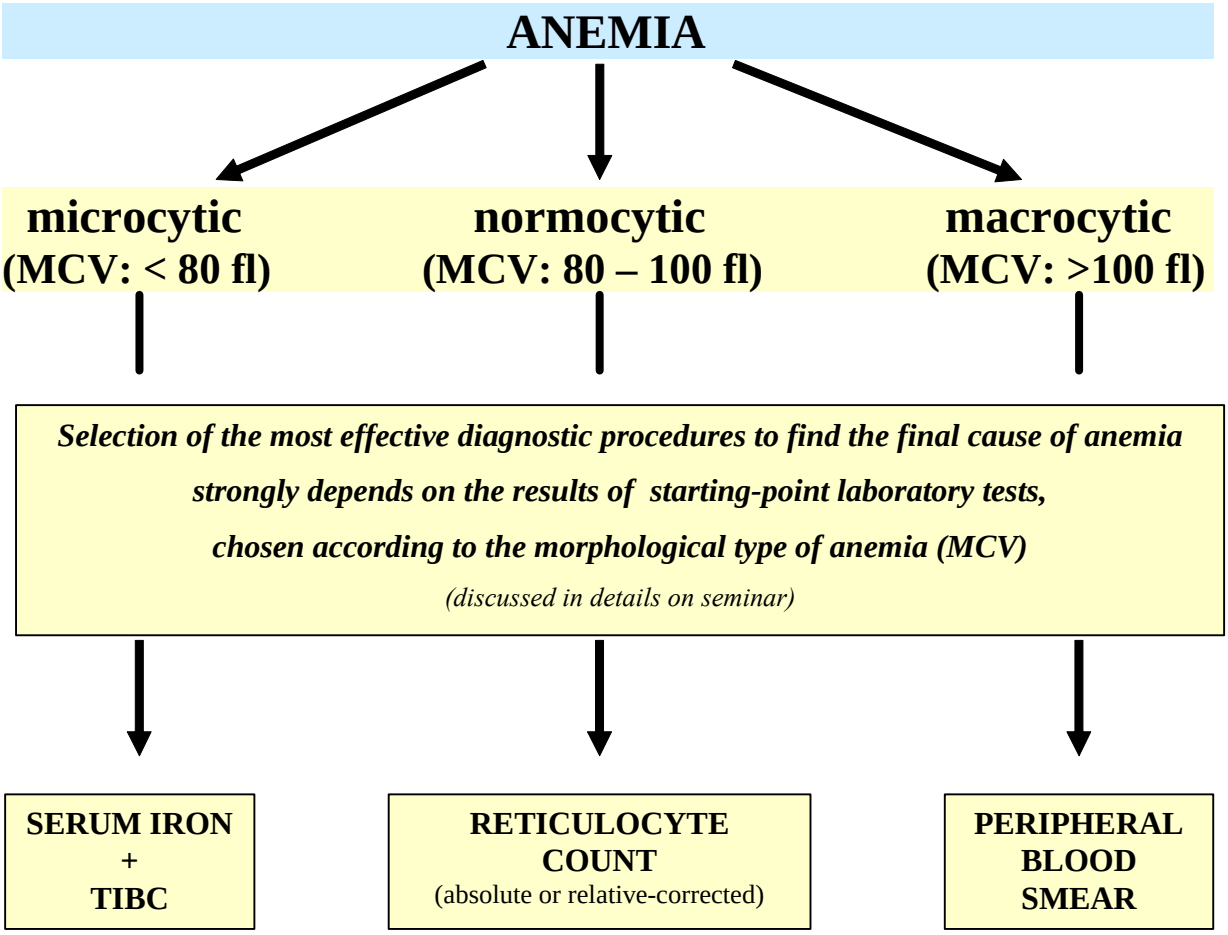
THALASSEMIA

IRON REUTILISATION DISORDER (Anemia of Chronic Disease - ACD)

To carry out the differential diagnosis of microcytic anemia start with evaluation of iron metabolism i.e. at least:
SERUM IRON + TIBC


ANEMIA
with
MCV: 80 – 100 fl
normocytic anemia
(usually also normochromic: MCH, MCHC = N)
Is bone marrow responding to reduced red blood cell mass by enhanced erythropoietic activity?
(is anemia of central or peripheral origin?)
RETICULOCYTE COUNT
(absolute or relative-corrected)
NORMAL OR DECREASED
ELEVATED
Associated leukocyte and platelet abnormalities?
Associated evidences (clinical and laboratory) for hemolysis?
YES
NO
NO
YES
Bone marrow disease, e.g.:
aplasia
fibrosis
malignancy
infiltration
myelodysplasia
Systemic disease (symptomatic anemia) affecting course of erythropoiesis by:
Decreased release of erythropoiesis activators, e.g.:
- uremia
- hypothyroidism
Increased release of erythropoiesis inhibitors, e.g.:
- anemia of chronic disease
Acute blood loss
Hemolytic anemia
Look for the cause: BONE MARROW EXAMINATION
Look for the specific laboratory features of clinically suspected systemic disease
The cause is usually obvious from the clinical findings
Look for the cause beggining from
BLOOD SMEAR


ANEMIA
with
MCV: > 100 fl
macrocytic anemia
Is blood film suggestive of megaloblastic anemia?
NO
YES
Is anything suggestive of megaloblastic anemia?
1. clinical picture
2. CBC
3. biochemical assays
YES
Consider:
BONE MARROW EXAMINATION
NO
Non-megaloblastic
(secondary macrocytic)
anemia
- alcohol, drugs
- liver disease
- hypothyroidism
- reticulocytosis
Megaloblastic
(primary macrocytic)
anemia
- history and clinical features usually indicate the likely cause
Follow the normocytic pathway and look for specific laboratory features of clinically suspected systemic disease
SERUM B12
AND
SERUM FOLATE and RED CELL ANALYSIS
NORMAL
- drug induced
- inborn metabolic errors
- myelodysplastic syndrome
FOLATE DEFICIENCY
B12 DEFICIENCY
ESTABLISH CAUSE



REFERENCES *(concerning both exercises devoted to hematology - I and II)*

1. Kumar, Abbas , Fausto (ed.): **Robins and Cotran Pathologic Basis of Disease** (7th ed.). Elsevier/Saunders 2005 – Chapters: 4 and 13.
2. Henry B J (ed.): **Clinical Diagnosis and Management by Laboratory Methods.** (20th ed.). W.B. Saunders Company 2001 – Chapters: 24-26 and 28-29.
3. Kasper, Braunwald, Fauci, Hauser, Longo, James (ed): **Harrison's principles of internal medicine.** (16th ed.). McGraw-Hill 2005 – Chapters: 52-53; 90-94; 101-103.
4. Gross S., Roath S. (ed.): **Hematology. A Problem - Oriented Approach**. Williams & Wilkins, Baltimore 1996.
5. Rodak B: **Diagnostic Hematology.** W.B. Saunders Company, Philadelphia 1995.
6. Isbister J.P. , Pittiglio D.H.: **Clinical Hematology. A Problem - Oriented Approach.** Williams & Wilkins, Baltimore 1988.

Basic laboratory tests in the diagnosis and management of haemostatic failure/
Wojciech Żak MD

HEMOSTASIS

=

the complex process including mechanisms which are to:

prevent blood loss from sites of vascular disruption

and

maintain blood fluency

=

DELICATE BALANCE

between

PROCOAGULANT MECHANISMS

forming clots
at sites of vascular damage:

PRIMARY HEMOSTASIS
=
formation of platelet plug

VESSELS — PLATELETS

INTERACTION

\+

PLASMA COAGULATION FACTORS

SECONDARY HEMOSTASIS
=
reinforcement of the platelet plug
by a meshwork of fibrin strands
=
COAGULATION

REGULATORY MECHANISMS

limiting clots formation
only to sites of vascular damage:

Regulation of PRIMARY HEMOSTASIS
=
prevention of platelet response
beyond the sites of vascular damage
by intact endothelial cells'
- *structure*
(negative charge of endothelial glycocalyx)
- *function*
(endothelial-derived substances:
prostacyclin, NO, ADPase)

Regulation of SECONDARY HEMOSTASIS
=
prevention of fibrin clot formation
beyond the sites of vascular damage
by endothelial-derived or activated substances:
- Tissue Factor Pathway Inhibitor (TFPI)
- Serine Protease Inhibitors (SERPINs)
- Protein C System
- Fibrinolytic System

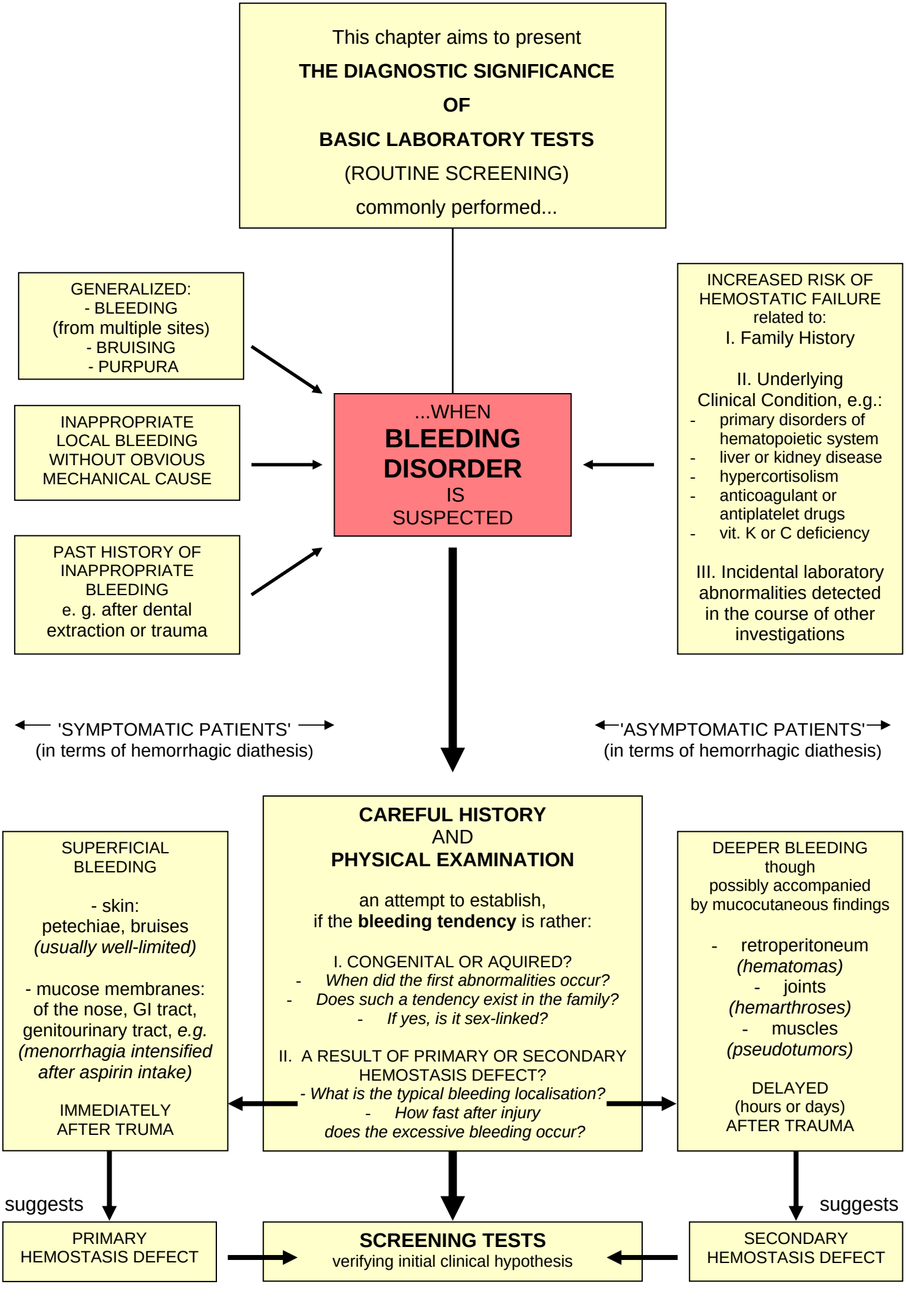
if this **BALANCE** is disturbed

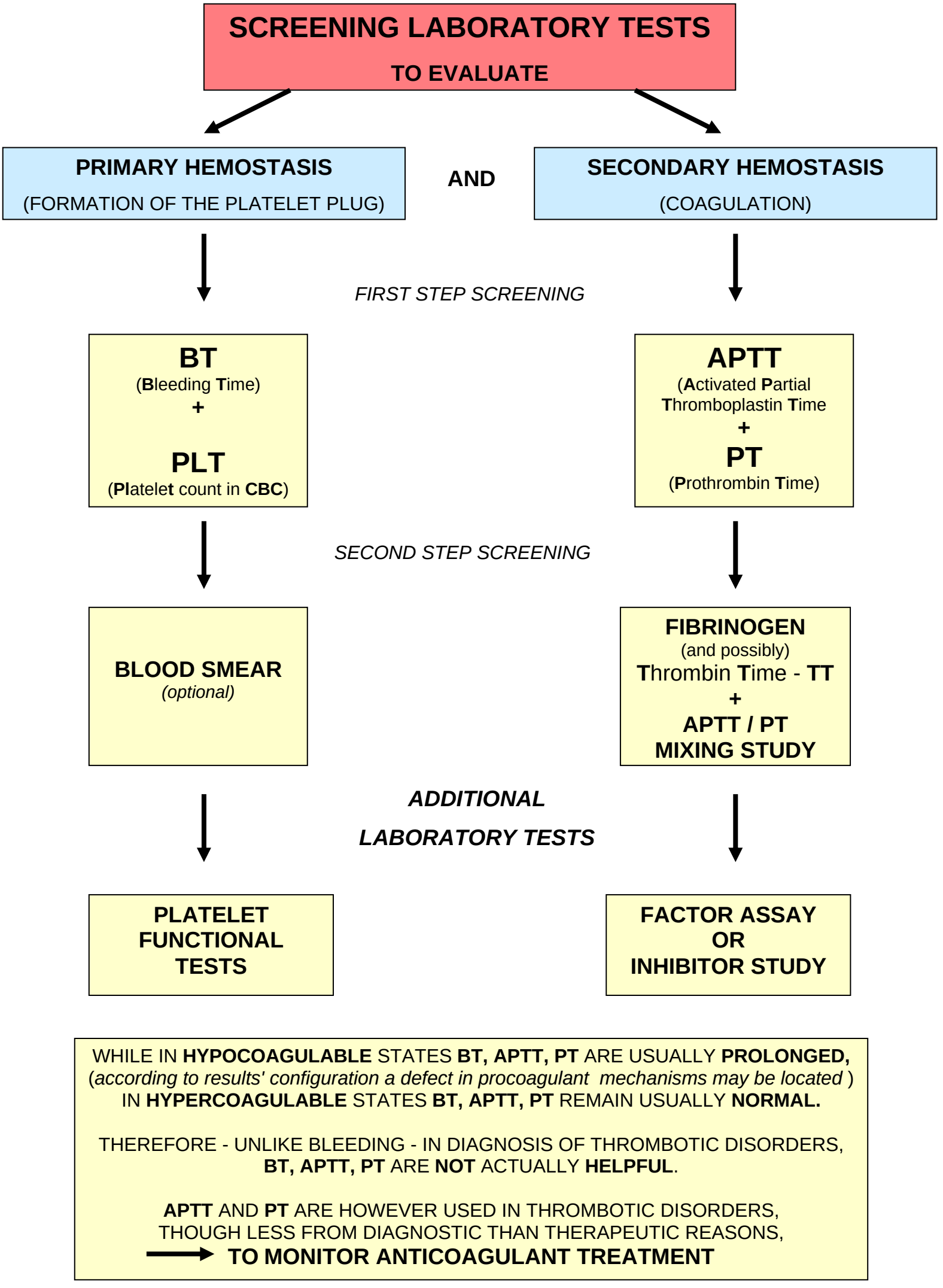
HYPOCOAGULABLE STATE
due to:
- *decreased procoagulant activity*
(e.g. deficiency of coagulation factors)
- *increased regulatory activity*
(e. g. fibrinolytic syndrome)

=
BLEEDING DISORDER

HYPERCOAGULABLE STATE
due to:
- *decreased regulatory activity*
(e. g. deficiency of natural anticoagulants)
- *increased procoagulant activity*
(clinical conditions leading to endothelial injury or/and abnormal blood flow; see: Virchow's triad)

=
THROMBOTIC DISORDER


This chapter aims to present
THE DIAGNOSTIC SIGNIFICANCE
OF
BASIC LABORATORY TESTS
(ROUTINE SCREENING)
commonly performed...
GENERALIZED:
- BLEEDING
(from multiple sites)
- BRUISING
- PURPURA
INAPPROPRIATE
LOCAL BLEEDING
WITHOUT OBVIOUS
MECHANICAL CAUSE
PAST HISTORY OF
INAPPROPRIATE
BLEEDING
e. g. after dental
extraction or trauma
...WHEN
BLEEDING
DISORDER
IS
SUSPECTED
INCREASED RISK OF
HEMOSTATIC FAILURE
related to:
I. Family History
II. Underlying
Clinical Condition, e.g.:
- primary disorders of hematopoietic system
- liver or kidney disease
- hypercortisolism
- anticoagulant or antiplatelet drugs
- vit. K or C deficiency
III. Incidental laboratory abnormalities detected in the course of other investigations
'SYMPTOMATIC PATIENTS'
(in terms of hemorrhagic diathesis)
'ASYMPTOMATIC PATIENTS'
(in terms of hemorrhagic diathesis)
CAREFUL HISTORY
AND
PHYSICAL EXAMINATION
an attempt to establish,
if the bleeding tendency is rather:
I. CONGENITAL OR AQUIRED?
- When did the first abnormalities occur?
- Does such a tendency exist in the family?
- If yes, is it sex-linked?
II. A RESULT OF PRIMARY OR SECONDARY HEMOSTASIS DEFECT?
- What is the typical bleeding localisation?
- How fast after injury does the excessive bleeding occur?
SUPERFICIAL
BLEEDING
- skin:
petechiae, bruises
(usually well-limited)
- mucose membranes:
of the nose, GI tract,
genitourinary tract, e.g.
(menorrhagia intensified after aspirin intake)
IMMEDIATELY
AFTER TRUMA
DEEPER BLEEDING
though
possibly accompanied
by mucocutaneous findings
- retroperitoneum
(hematomas)
- joints
(hemarthroses)
- muscles
(pseudotumors)
DELAYED
(hours or days)
AFTER TRAUMA
suggests
suggests
PRIMARY
HEMOSTASIS DEFECT
SCREENING TESTS
verifying initial clinical hypothesis
SECONDARY
HEMOSTASIS DEFECT



WHILE IN **HYPOCOAGULABLE** STATES **BT, APTT, PT** ARE USUALLY **PROLONGED,**
(*according to results' configuration a defect in procoagulant mechanisms may be located*)
IN **HYPERCOAGULABLE** STATES **BT, APTT, PT** REMAIN USUALLY **NORMAL.**

THEREFORE - UNLIKE BLEEDING - IN DIAGNOSIS OF THROMBOTIC DISORDERS,
BT, APTT, PT ARE **NOT** ACTUALLY **HELPFUL**.

APTT AND **PT** ARE HOWEVER USED IN THROMBOTIC DISORDERS,
THOUGH LESS FROM DIAGNOSTIC THAN THERAPEUTIC REASONS,
→ **TO MONITOR ANTICOAGULANT TREATMENT**

ONE COULD HARDLY UTILIZE THE SCREENING TESTS
IN THE DIAGNOSIS OF BLEEDING DISORDERS
WITHOUT GOOD UNDERSTANDING OF HEMOSTASIS
(at least to the extant it is evaluated by these tests)

SO, WILLY NILLY, WE HAVE TO FOLLOW IT!

VASCULAR DISRUPTION INITIATES SIMULTANEOUSLY...

3 PROCESSES

PLATELET - VASCULAR INTERACTION

TO FORM
A PLATELET PLUG

initiated by platelets ' adhesion to exposed subendothelial tissue

PRIMARY HEMOSTASIS

INTRINSIC COAGULATION PATHWAY
(all components are found in the circulating blood)

TO FORM THROMBIN
with subsequent
FIBRINOGEN TO FIBRIN
CONVERSION

*initiated by binding of contact group factors **(XII, XI, HMWK, PK)** to negatively charged surfaces of collagen and activated platelets*

EXTRINSIC COAGULATION PATHWAY
(requires a component normally absent in the circulating blood)

TO FORM THROMBIN
with subsequent
FIBRINOGEN TO FIBRIN
CONVERSION

*initiated by blood occurrence of **tissue factor (TF) -** a membrane glycoprotein coming from subendothelial and surrounding tissues*

SECONDARY HEMOSTASIS

EVALUATED BY

BT | **APTT** | **PT**

THE DIAGNOSTIC SIGNIFICANCE OF EACH OF THESE TESTS WILL BE PRESENTED ON FOLLOWING PAGES, AGAINST THE BACKGROUND OF THE ADEQUATE PART OF HEMOSTASIS. DIFFERENT CONFIGURATIONS OF ABNORMAL RESULTS IN CONTEXT OF CLINICAL PICTURE AS A STARTING-POINT OF BLEEDING DISORDERS' DIFERENTIAL DIAGNOSIS ARE DISCUSSED DURING EXERCISES.
PARTICULAR ATTENTION IS PAID TO THE COMMONEST CAUSES OF HEMORRHAGIC DIATHESES, SUCH AS:

	PRIMARY ←	HEMOSTASIS DEFECT	→ SECONDARY
CONGENITAL	**von Willebrand's Disease**		**Hemophilia A**
AQUIRED	**Thrombocytopenia**		**Liver Disease** **Vitamin K Deficiency**

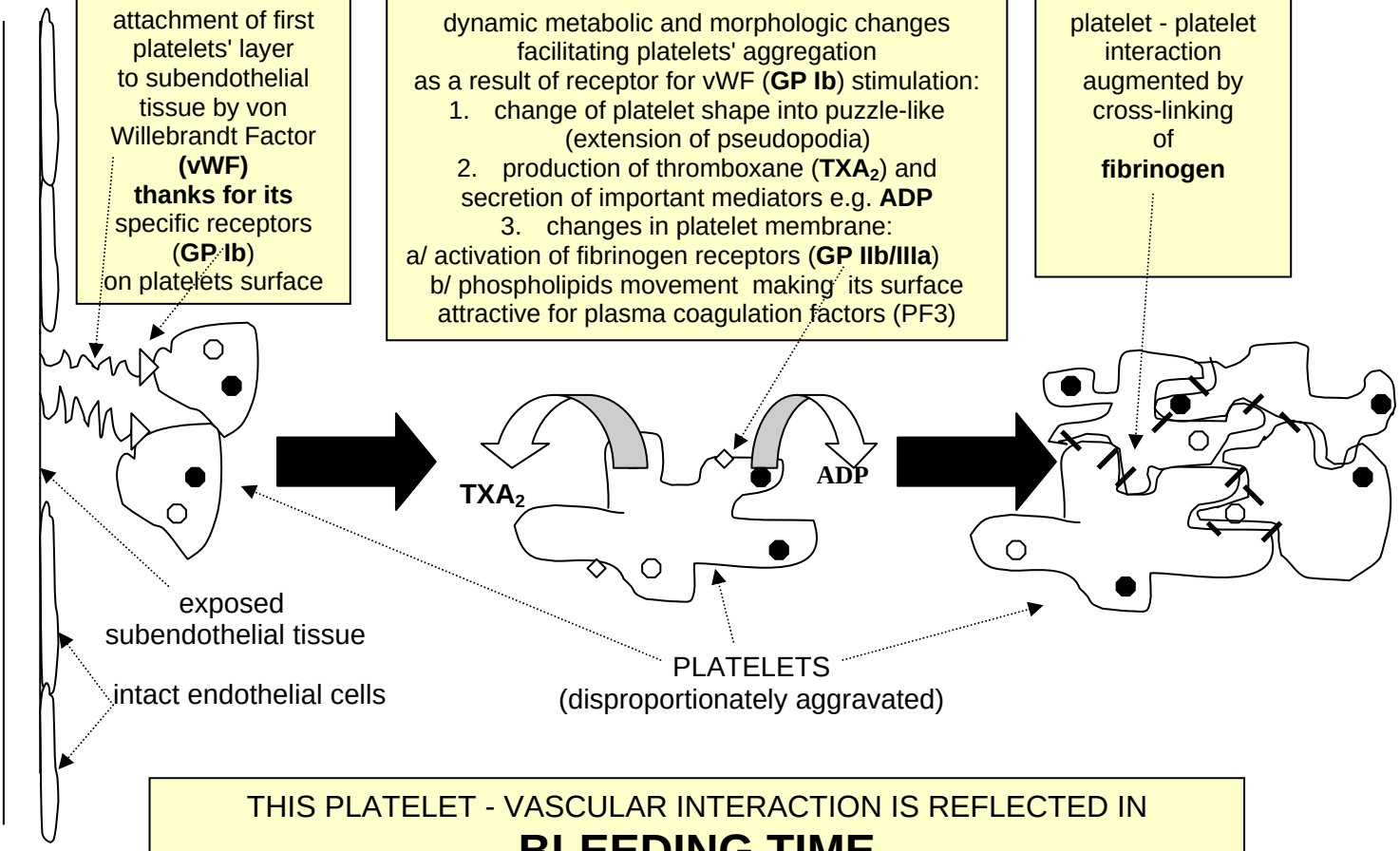
PRIMARY HEMOSTASIS
=
FORMATION OF PLATELET PLUG
(+VASOCONSTRICTION)
TO ARREST BLEEDING AS QUICKLY AS POSSIBLE

THERE ARE 3 MAJOR STEPS (**3** X **A**)
OF PLATELET RESPONSE TO VASCULAR INJURY

ADHESION
=
attachment of first platelets' layer to subendothelial tissue by von Willebrandt Factor **(vWF)** **thanks for its** specific receptors (**GP Ib**) on platelets surface

ACTIVATION
=
dynamic metabolic and morphologic changes facilitating platelets' aggregation as a result of receptor for vWF (**GP Ib**) stimulation:
1. change of platelet shape into puzzle-like (extension of pseudopodia)
2. production of thromboxane (**TXA_2**) and secretion of important mediators e.g. **ADP**
3. changes in platelet membrane:
a/ activation of fibrinogen receptors (**GP IIb/IIIa**)
b/ phospholipids movement making its surface attractive for plasma coagulation factors (PF3)

AGREGATION
=
platelet - platelet interaction augmented by cross-linking of **fibrinogen**



THIS PLATELET - VASCULAR INTERACTION IS REFLECTED IN
BLEEDING TIME
THEREFORE BT IS USUALLY PROLONGED IN A DEFECT OF:

I. PLATELETS:
- Ia. quantitative - thrombocytopenia
- Ib. qualitative - hereditary or acquired platelet dysfunction

II. VESSELS - hereditary or acquired vascular disorders

III. INTERACTION (itself), at the stage of:
- IIIa. **A**DHESION: von Willebrand's Disease
- IIIb. **A**CTIVATION: (besides Ib) NSAID or other antiplatelet drugs
- IIIc: **A**GREGATION: severe hypo- or dysfibrinogenemia

CAUTION!!!
Apart from factor I (fibrinogen), deficiency of any coagulation factor (e. g. hemophilia) DO NOT PROLONG BLEEDING TIME,
SINCE IT ONLY REFLECTS PRIMARY BUT NOT SECONDARY HEMOSTASIS!

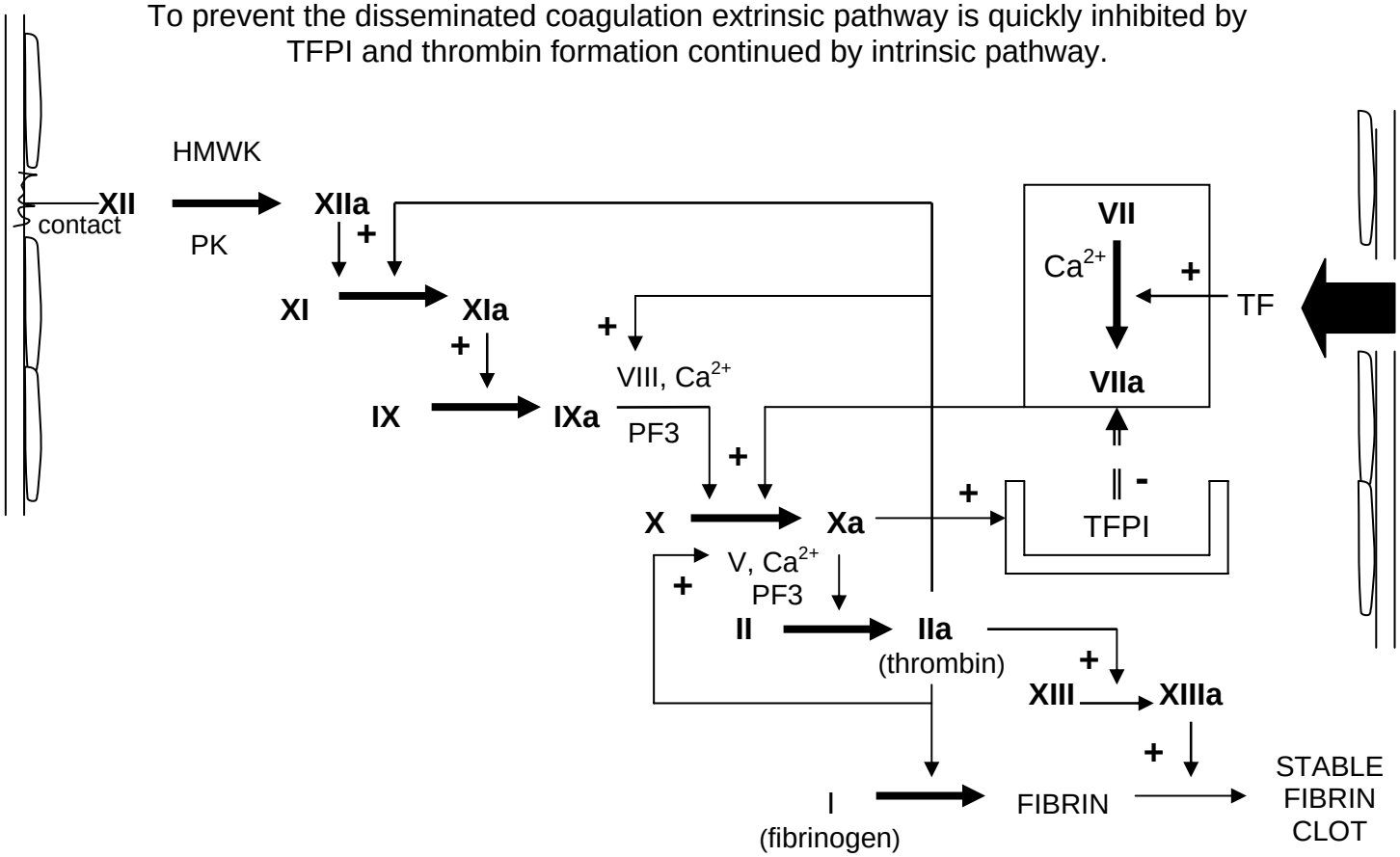
SECONDARY HEMOSTASIS
=
REINFORCEMENT AND STABILIZATION OF PLATELET PLUG
AT THE SITE OF VASCULAR DISRUPTION
BY FORMATION OF FIBRIN CLOT

TWO MAJOR PHASES:

I. FORMATION OF THE POTENT PROCOAGULANT ENZYME - **THROMBIN**
in multiple enzymatic steps collectively known as
COAGULATION CASCADE

II. CONVERSION OF SOLUBLE PROTEIN - **FIBRINOGEN**
N INTO INSOLUBLE GEL OF **FIBRIN** MESHWORK

Although both intrinsic and extrinsic pathways are simultaneously activated, the **extrinsic** one is nowadays regarded to play a **major physiological role** in initiating the coagulation cascade.
Plasma occurrence of TF rapidly generates a trace amount of thrombin, which significantly facilitates the course of intrinsic pathway (by activation of its pivotal cofactors, e.g. V and VIII, and factor XI).
To prevent the disseminated coagulation extrinsic pathway is quickly inhibited by TFPI and thrombin formation continued by intrinsic pathway.



INTRINSIC PATHWAY → ← EXTRINSIC PATHWAY

SERINE PROTEASES : FACTORS **XII, XI** + vitamin K-dependent FACTORS (**X, IX, VII, II**)
OTHER ENZYMES: FACTOR **XIII** (transglutaminase stabilizing fibrin clot)
COFACTORS:
- HMWK (High Molecular Weight Kininogen),
- PK (Prekalikrein)
- PF3 (phospholipids on activated platelets' surface)
- FACTORS VIII, V and IV (Ca)

OTHER FACTORS: FACTOR III (**T**ISSUE **F**ACTOR - TF), FACTOR I (FIBRINOGEN)

LABORATORY EVALUATION OF SECONDARY HEMOSTASIS

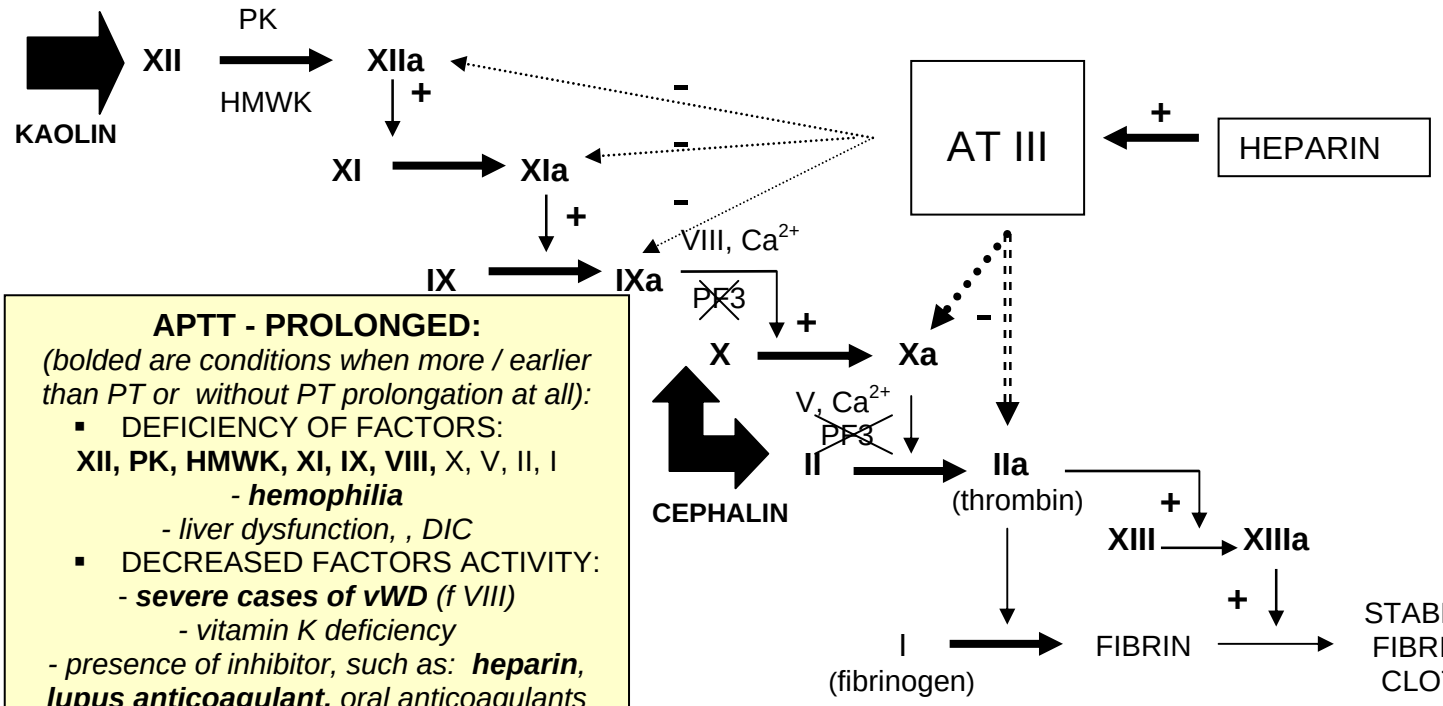
The idea is to induce and examine in vitro (in patient's citrated plasma)
either intrinsic or extrinsic pathway, separately.
Calcium ions - the necessary cofactor for both pathways -
had been previously inhibited by citrate to prevent a spontaneous coagulation.
So to induce it later under controlled circumstances Ca must be added (citrate chloride) to plasma
along with substances of similar properties to specific activators for each pathway in vivo.

to check intrinsic or extrinsic pathway → citrated plasma + $CaCl_2$ + <u>SPECIFIC ACTIVATORS</u>

ISOLATED **PRIMARY HEMOSTASIS DEFECT** (DUE TO PLATELETS, VESSELS or INTERACTION)
DOES NOT PROLONG THESE TIMES!!!

INTRINSIC PATHWAY - APTT (**A**ctivated **P**artial **T**hromboplastin **T**ime) =

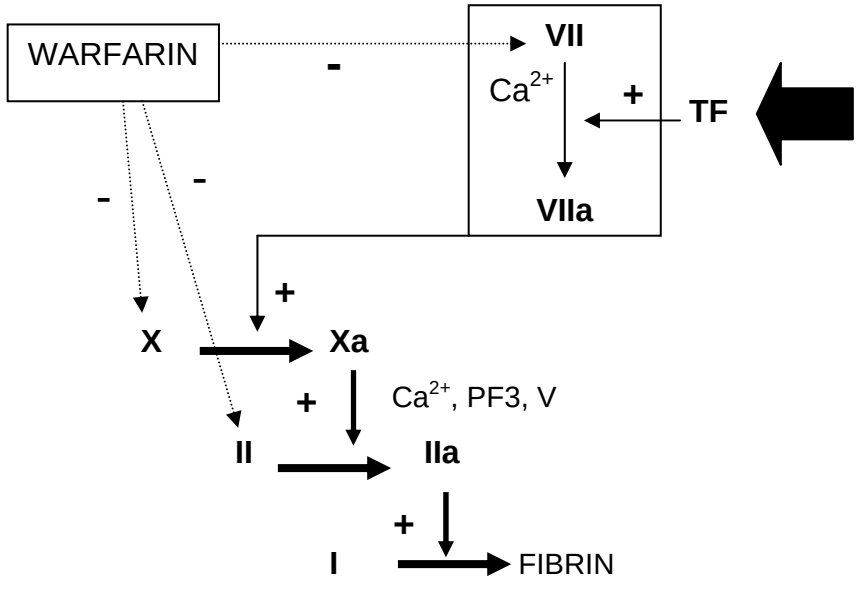
CITRATED PLASMA + $CACl_2$ + ACTIVATORS (specific for intrinsic pathway), i. e:
- some negatively charged surface (instead of collagen), e. g. kaolin
- some phospholipids (instead of PF3) – "partial thromboplastin", e. g. cephalin



APTT - PROLONGED:
(bolded are conditions when more / earlier than PT or without PT prolongation at all):
- DEFICIENCY OF FACTORS:
XII, PK, HMWK, XI, IX, VIII, X, V, II, I
- ***hemophilia***
- liver dysfunction, , DIC
- DECREASED FACTORS ACTIVITY:
*- **severe cases of vWD** (f VIII)*
- vitamin K deficiency
*- presence of inhibitor, such as: **heparin**, **lupus anticoagulant,** oral anticoagulants*

EXTRINSIC PATHWAY – PT (**P**rothrombin **T**ime) =

CITRATED PLASMA + $CACl_2$ + ACTIVATOR (specific for extrinsic pathway), i. e:
- "full thromboplastin" = tissue extract (e.g. from the brain) = TF + phospholipids



PT - PROLONGED:
(bolded are conditions when more / earlier than APPT or without APTT prolongation):

- DEFICIENCY OF FACTORS:
VII, X, V, II, I
- ***liver dysfunction**, , DIC*
-
- DECREASED FACTORS ACTIVITY:
*- **vitamin K deficiency***
- presence of inhibitor, such as:
heparin
*lupus anticoagulant**, oral anticoagulants***

APTT / PT RESULTS IN CONFIGURATION - SUMMARY

APTT	PT	***CAUSES*** *and EXPLANATIONS*
↑	**N**	***DEFICIENCIES or DECREASED ACTIVITY OF FACTORS***: ▪ ***VIII:*** *- hemophilia A,* *- severe cases of von Willebrand's disease (vWF = carrier for f VIII)* *- circulating inhibitor of factor VIII* *(supplemental treatment of hemophilia A or post partum)* ▪ ***IX*** *(hemophilia B),* ▪ ***XI*** *(hemophilia C)* ▪ *XII, HMWK, PK – no affect on clotting in vivo – no bleeding!!!*
↑	**↑ or N**	▪ ***lupus anticoagulant*** *– inhibits phospholipids (replacing PF3)*
↑	↑	▪ ***heparin treatment*** *– by activating ATIII inhibits factors:* ***IIa Xa IXa, XIa, XIIa***
N	↑	***DEFICIENCY OF FACTOR VII*** ▪ ***hereditary*** *(rare)* ▪ ***early stage of liver disease -*** *although almost all coagulation factors are produced in the liver, decreased synthesis particularly affects f. VII, since its most rapid turnover, thus it is earlier reflected in PT than APTT*
↑	↑	***DEFICIENCY OF FACTOR VII*** ***and*** ***FACTORS LOCATED IN COMMON PATHWAY*** *(I, II, V, X)* ▪ ***vitamin k deficiency / oral anticoagulants*** *- in both conditions the activity of vitamin K - dependent factors (II, VII, IX, X) as well as protein C and S is decreased; for the reasons mentioned above it particularly affects f. VII* ▪ ***intermediate stage of liver disease evolution***
↑	↑	***MULTIPLE FACTOR DEFICIENCIES*** ▪ ***advanced liver disease*** ▪ ***DIC***

CONFIGURATIONS OF SCREENING LABORATORY TESTS RESULTS IN THE MOST COMMON BLEEDING DISORDERS

DISORDER	BT	PLT	APTT	PT	Fibrinogen
thrombocytopenia	↑	↓	N	N	N
thrombocytopathy (e.g. Glanzmann thrombastenia)	↑	N	N	N	N
von Willebrand's disease	↑	N	N / ↑	N	N
hemophilia	N	N	↑	N	N
heparin treatment	N	N	↑	↑	N
oral anticoagulants	N	N	↑	↑	N
advanced liver disease (numbers indicate the sequence of events)	4 ↑	5 ↓	2 ↑	1 ↑	3 ↓
DIC (advanced stage)	↑	↓	↑	↑	↓

The evaluation of acid-base balance in clinical practice

Waldemar Myszka MD

Key definitions and formulas for clinical acid-base problem solving

Rule 1. Determine pH status (alkalemia or academia)

Rule 2. Determine whether the primary process is respiratory, metabolic or both.

Alkalosis

- Respiratory Alkalosis: if pCO_2 substantially less than 35 mmHg
- Metabolic Alkalosis: if bicarbonate grater than 26 mmol/L

Acidosis

- Respiratory Acidosis: if pCO_2 grater than 45 mmHg
- Metabolic Acidosis: if bicarbonate less than 22 mmol/L

Rule 3. Calculate the serum anion gap

Anion gap = Sodium – (Bicarbonate + Chloride)

- Anion gap that is increased (greater than 10 mEq/L can indicate metabolic acidosis
- Anion gap increased beyond 20 mEq/L always indicates a metabolic acidosis
- For every 1 g/dL albumin below normal add 2,5 to the calculated anion gap

Rule 4. Check the degree of compensation

Metabolic Acidosis

- $Pco_2 = 1.5x(HCO_3^-) + 8 \pm 2$
- P_{CO2} falls by 1 – 1.3 mmHg for each mEq/L fall in (HCO_3^-)
- Last 2 digits of pH = P_{CO2} (thus if P_{CO2} = 28, pH = 7.28)

Metabolic Alkalosis

- Pco_2 increases 6 mmHg for each 10 mEq/L rise in HCO_3^-
- $HCO_3^- + 15 = pCO_2$

Respiratory Acidosis

Acute: HCO_3^- increases by 1 mEq/L for each 10 mmHg rise in Pco_2

Chronic: HCO_3^- increases by 4 mEq/L for each 10 mmHg rise in Pco_2

Respiratory Alkalosis

Acute: HCO_3^- falls by 2 mEq/L for each 10 mmHg fall in Pco_2

Chronic: HCO_3^- falls by 4 for each 10 mmHg fall in Pco_2

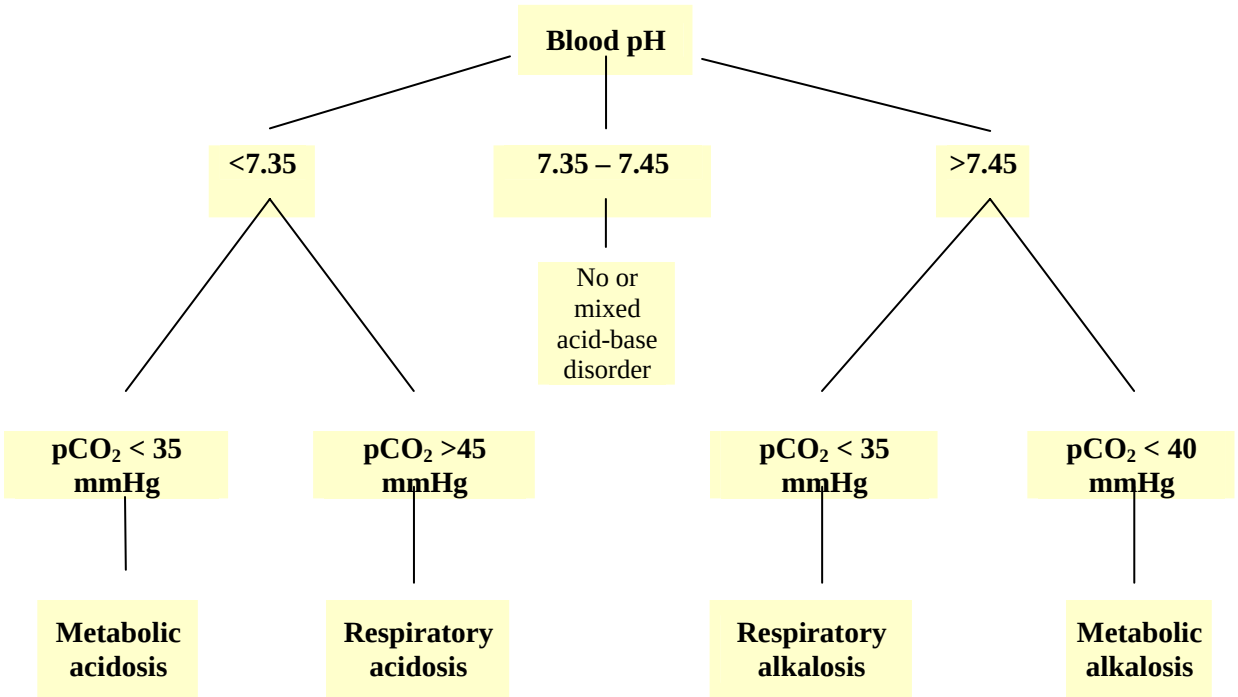
Rule 5. Determine whether there is a 1:1 relationship between anions in blood (also called delta gap)

Refers to increased anion gap metabolic acidosis

Normal values of tests utilized for acid-base problem solving

Arterial blood gases	**pH** – 7.35-7.45 **pO_2** – 8.7-12.7 kPa (65-95 mmHg) **pCO_2** – 4.8-6.0 kPa (35-45 mmHg) **HCO_3^-** – 22-26 mmol/l **BE** – ± 2.5 mmol/l
Anion gap	**AG** - 3 – 12 mEq/l
Plasma electrolytes concentration	**Na^+** – 135-145 mmol/l **K^+** – 3.5-5.0 mmol/l **Cl^-** – 98-107 mmol/l **HCO_3^-** – 22-26 mmol/l **Ca** – 2.12-2.62 mmol/l (8.5-10.5 mg/dl) **Ca^{2+}** – 0.98-1.13 mmol/l **Mg^{2+}** – 0.8-1.0 mmol/l (1.9-2.5 mg/dl) **PO_4^{2-}** – 0.97-1.45 mmol/l (3.0-4.5 mg/dl)
Urine electrolytes daily excretion	**Na^+** –80-240 mmol/24 h **K^+** – 25-80 mmol/24 h **Cl^-** – 110-260 mmol/24 h
Albumin	35-50 g/l

Classification of the primary acid-base disorders based on arterial blood pH and pCO_2 tension findings



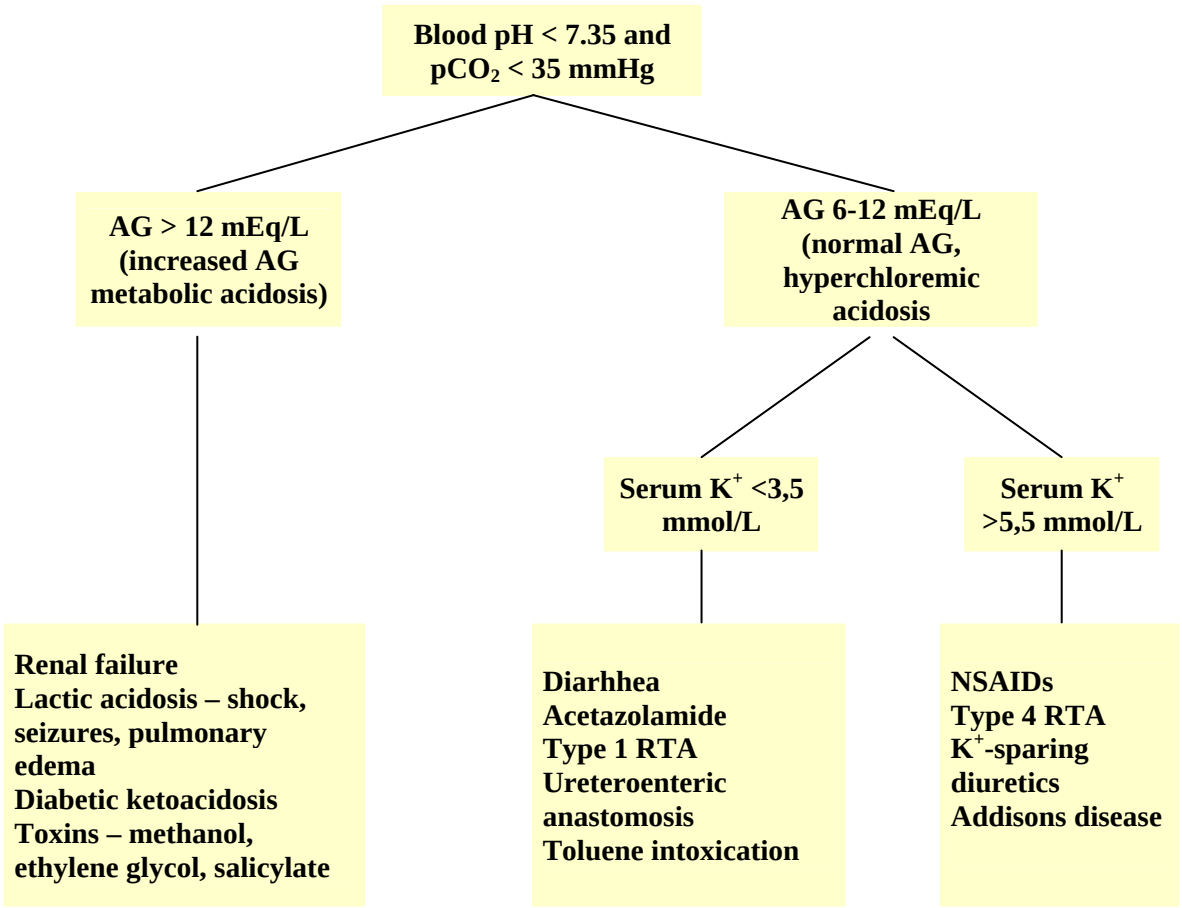
Relations between three parameters describing acid-base balance

	pH	HCO_3^-	pCO_2
Metabolic acidosis	↓	(↓)	↓
Metabolic alkalosis	↑	(↑)	↑
Respiratory acidosis	↓	↑	(↑)
Respiratory alkalosis	↑	↓	(↓)

Note: primary changes leading to pH alterations are circled

Metabolic acidosis

Classification based on the serum anion gap (AG) and K^+ concentration



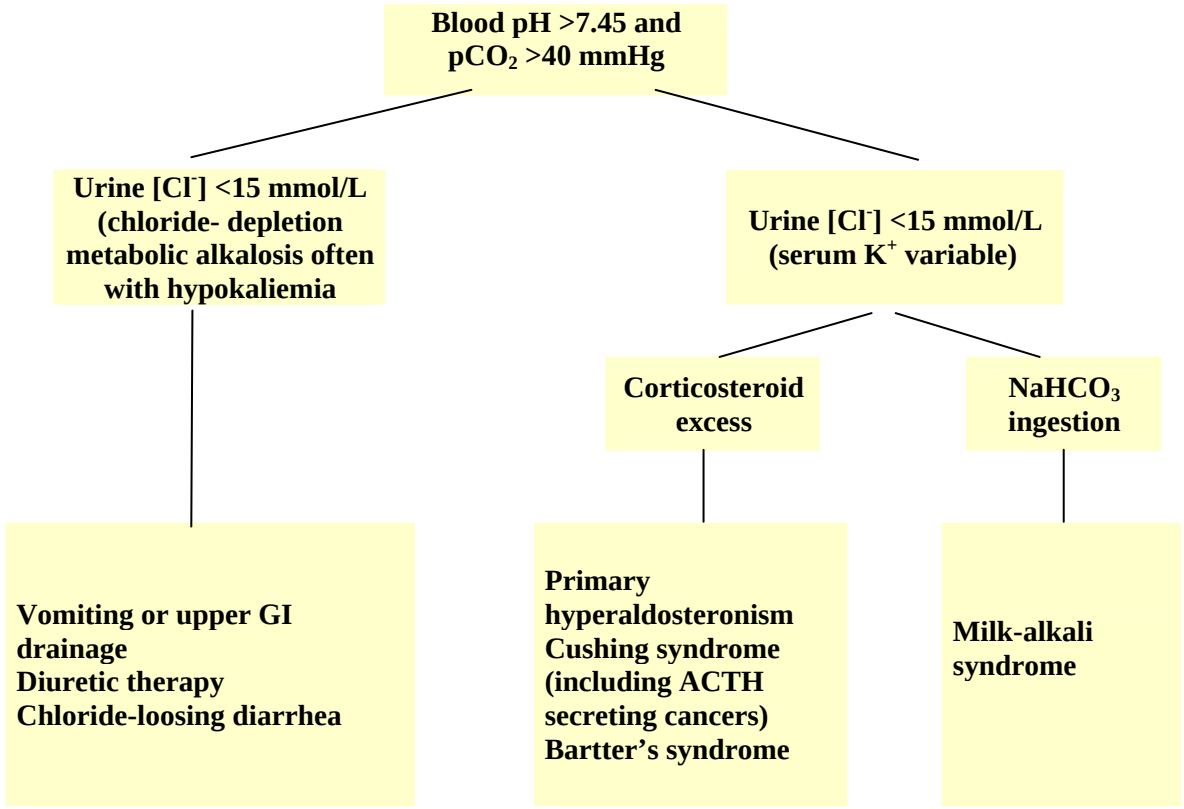
Principles of treatment of metabolic acidosis

1. Assess the severity of disorder - mild disturbances may have little clinical significance and require no corrective therapy. If the underlying cause can be treated effectively, there is often no need for specific therapy of the acid-base disorder.
2. When specific treatment is indicated, complete correction of the disturbance is usually not necessary. The goal is to correct the disorder toward normal and allow the body to make the fine adjustments itself.
3. The acuteness and severity of the disorder often determines the rapidity and aggressiveness with which is should be corrected.
4. The acid-base status must be monitored frequently and the treatment modified according to the patient's response.
5. The use of the alkali is frequently recommended when the arterial pH is less than 7.2 or the serum bicarbonate is 12 mEq/L or less.
6. Metabolic acidosis should not be corrected aggressively (if not pH of the CSF may decrease further leading to obtundation, convulsion, coma).
7. Remember: it is crucial to monitor serum potassium levels when acid-base disorders are corrected.
8. Estimation of bicarbonate required for correction of acidosis:

$[HCO_3^-]$ deficit = [24 mEq/L – measured HCO_3^-]x 0.5x body weight

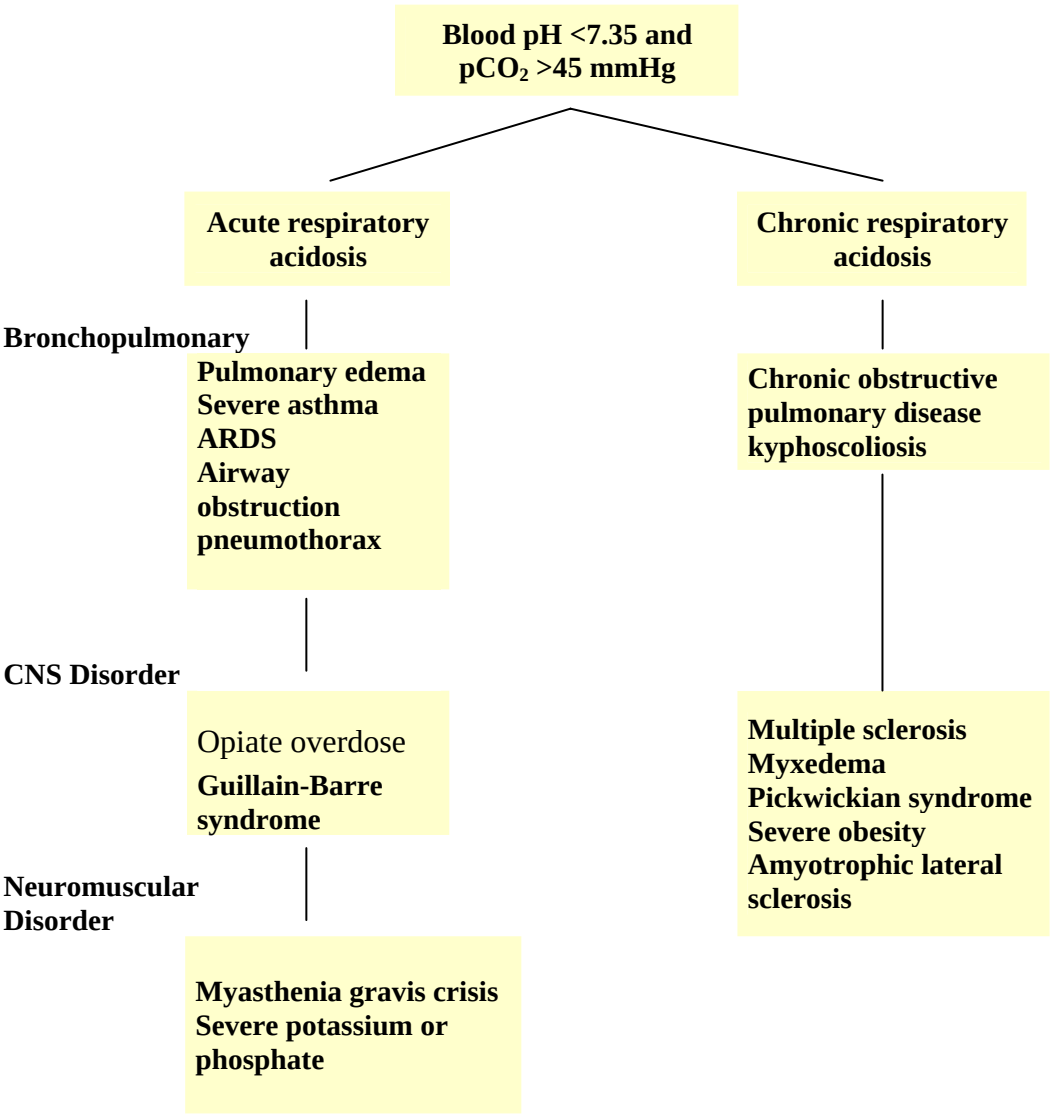
One half of the calculated deficit may be replaced in 3 to 4 hours in concentration 50 – 150 mEq/L

Metabolic alkalosis
Classification based on whether the cause is chloride depletion (with low urinary $[Cl^-]$ or not)

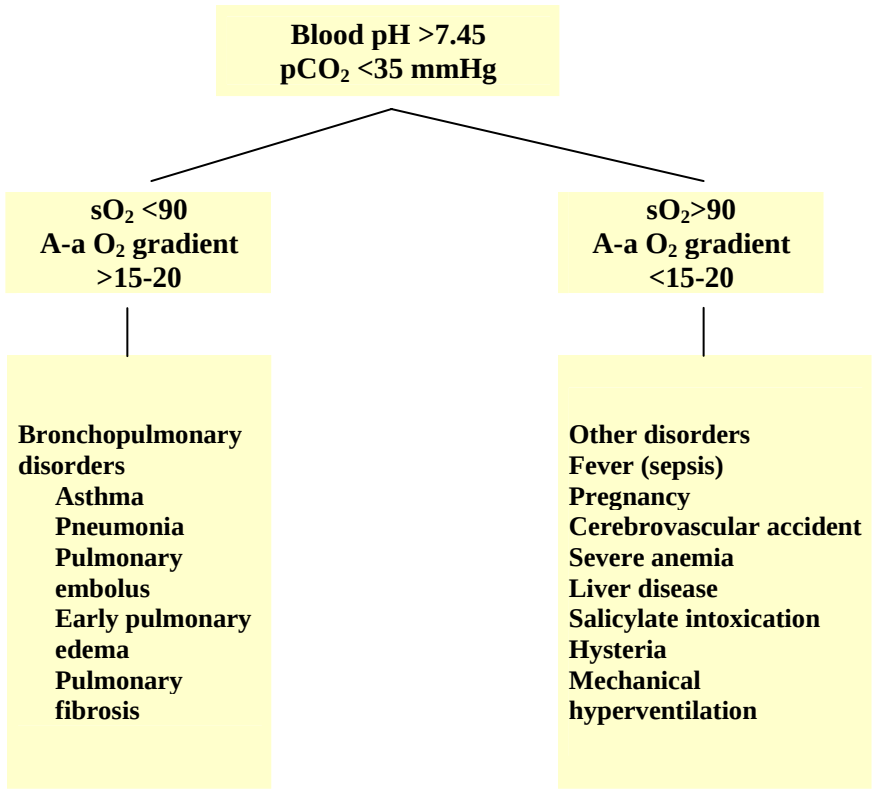


Respiratory acidosis

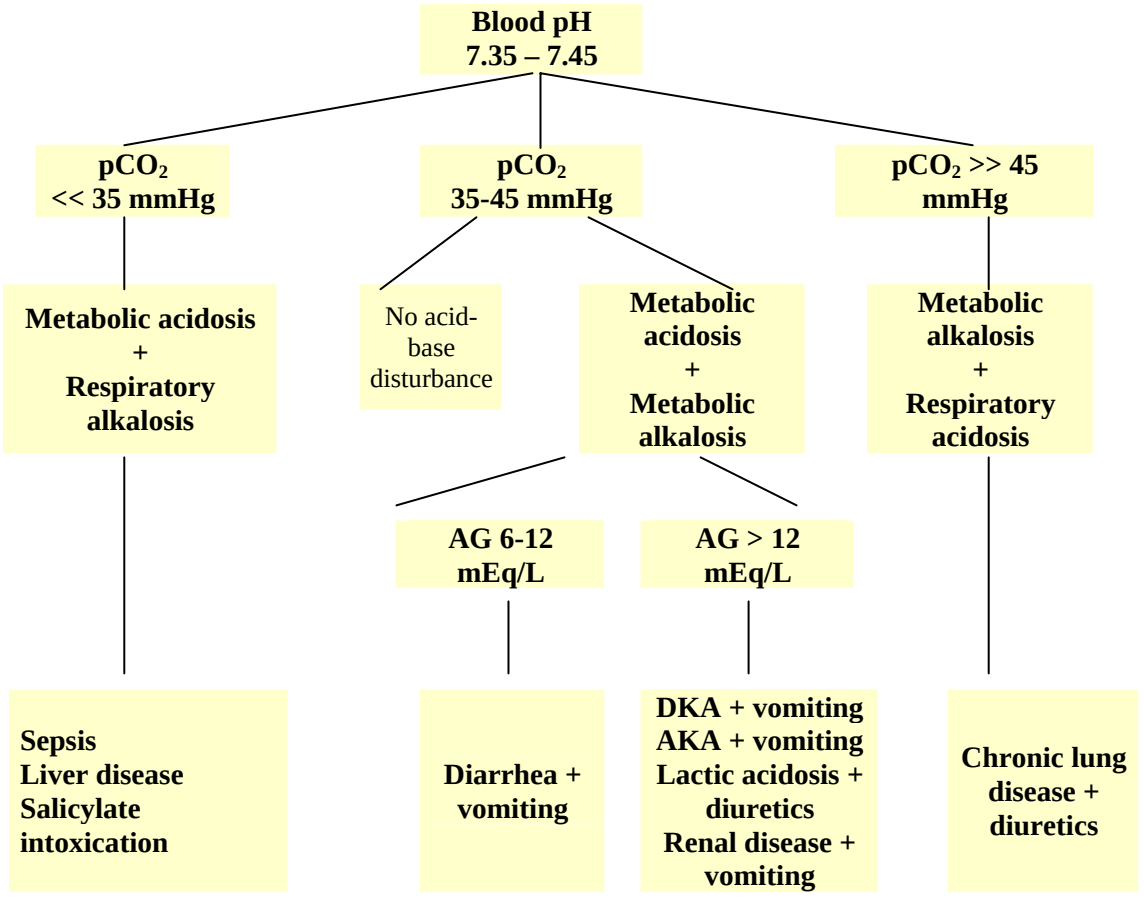
Classification based on whether the problem is acute or chronic and then whether there is a chest, central nervous system, or peripheral neuromuscular disorder



Respiratory alkalosis
Classification based on whether there is hypoxemia and an increased A-a (alveolo-arterial) oxygen gradient



Mixed acid-base disorders
Classification based on arterial blood pH and CO_2 tension findings



References:

1. B.D. Rose: *Clinical physiology of acid-base and electrolyte disorders*. McGraw-Hill Health Professions Division 2001
2. Harrison's Principles of Internal Medicine. 14th ed. McGraw-Hill. 1998.
3. Henry J.B. Clinical Diagnosis and Management by Laboratory Methods. 19th ed. W.B. Saunders Company. Philadelphia 1996.
4. Ravel R. Clinical Laboratory Medicine. Clinical Application of Laboratory Data. 6th ed. Mosby-Year Book. 1995.

Diagnostic approach to water-electrolyte disturbances

Waldemar Myszka MD

The following are required to assess water and electrolyte status of a patient

Past history

↓

Physical examination

↓

Laboratory findings

↓

Fluid chart i.e. daily record of water intake and loss.

This is essential for monitoring patients with water and electrolyte disorders and those treated with intravenous fluids.

Laboratory tests that are useful in the diagnosis of water-electrolyte balance disorders – reference values			
Blood (plasma)			**Urine**
Electrolytes	**Na^+** – 135-145 mmol/l **K^+** – 3.5-5.0 mmol/l **Cl^-** – 98-107 mmol/l **HCO_3^-** – 21-26 mmol/l **Ca** – 2.12-2.62 mmol/l (8.5-10.5 mg/dl) **Ca^{2+}** – 0.98-1.13 mmol/l **Mg^{2+}** – 0.8-1.0 mmol/l (1.9-2.5 mg/dl) **PO_4^{2-}** – 0.97-1.45 mmol/l (3.0-4.5 mg/dl)	**Electrolytes**	<u>Daily excretion</u> **Na^+** – 80-240 mmol/l **K^+** – 25-80 mmol/l **Cl^-** – 110-260 mmol/l
Kidney function	**Urea** – 2.5-6.4 mmol/l (15-39 mg/dl) **BUN –** 7-18 mg/dl **Creatinine** – 62-124 μmol/l (0.7-1.4 mg/dl)		
Acid-base status	**pH** – 7.35-7.45 **pO_2** – 8.7-12.7 kPa (65-95 mmHg) **pCO_2** – 4.8-6.0 kPa (35-45 mmHg) **HCO_3^-** – 22-26 mmol/l **BE** – ± 2.5 mmol/l		
CBC	**HGB** – M: 14-18 g/dl, F: 12-16 g/dl **HCT** – M: 42-52 %, F: 37-47% **RBC** – M: 4.7-6.1 $x10^{12}$/l , F: 4.2-5.4 $x10^{12}$/l **MCV** – M: 80-94 fl, F: 81-99 fl **MCH** – M: 27-31 pg, F: 27-31 pg **MCHC** – M: 33-37 g/dl, F: 33-37 g/dl **WBC** – M: 4.8-10.8 x 10^9/l, F: 4.8-10.8x 10^9/l **PLT**– 130-400$x10^9$/l		
Other biochemical tests	**Protein (total)**– 60-80 g/l **Albumin** – 35-50 g/l **Glucose –** 65-110 mg/dl		

Electrolyte content of body fluids

	Na^+ mEq/L	K^+ mEq/L	Cl^- mEq/L	HCO_3^- mEq/L
Plasma	142	4.5	102	26
Saliva	33	20	34	0
Gastric juice	60	9	84	0
Bile	149	4.9	101	45
Pancreatic juice	141	4.6	77	92
Small bowel	105	5.1	99	50
Ileal fluid	129	11.2	116	29
Fecal fluid	80	21	48	22
Cerebrospinal fluid	141	2.9	127	23
Sweat	45	4.5	58	0

Approximate electrolyte content in mEq/L of carbohydrate and saline solutions

Solution	Na^+	Cl^-	mOsm/L
Saline solution			
0.45%	**77**	**77**	**154**
0.9%	**154**	**154**	**308**
3%	**513**	**513**	**1026**
Dextrose in water			
5%			**253**
10%			**505**
20%			**1010**
40%			**2526**
70%			**3536**
Dextrose in saline			
5% in 0.22%	**38**	**38**	**330**
5% in 0.45%	**77**	**77**	**406**
5% in 0.9%	**154**	**154**	**559**

Concentration of ions in mEq/L of polyionic solutions

Solution	Na^+	K^+	Ca^{2+}	Cl^-	HCO_3^- precursor
Ringer's lactated	147	4	5	156	-
Hartmann's	130	4	3	109	28

Potassium content in 1 mL of chosen potassium preparations

Potassium chloride 1-3 mEq/mL
Potassium acetate 2-4 mEq/mL
Potassium phosphate 2 mEq/mL

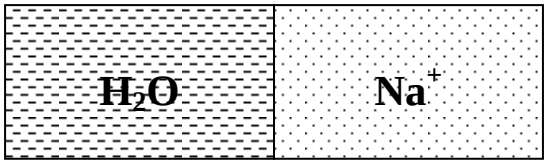
Concentration of ions in alkalizing preparations (in mEq/L)

Solution	**Na^+**	**HCO_3^-**
Sodium bicarbonate 1.96%	150	150
Sodium bicarbonate 8.4%	1000	1000

Disorders of water-sodium balance

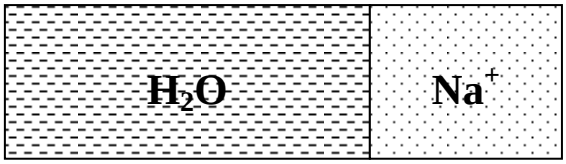
Disorders of water balance

Disorders of water balance are reflected in changes of osmolality



Na^+ 135 – 145 mmol/l
P_{Osm} 285 – 295 mOsm/kg_{H2O}

Normally there is such a proportion of water to sodium in the extracellular fluid (ECF) that sodium concentration in that compartment ranges from 135 to 145 mmol/l. As sodium is the most abundant cation in the ECF it is responsible for plasma osmolality which in this case ranges from 285 to 295 mOsm/kg_{H2O}



Na^+<135 mmol/l
P_{Osm} <285 mOsm/kg_{H2O}

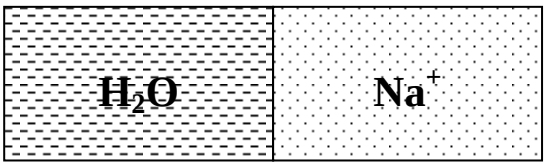
The relative water excess leads to Na dilution. Sodium concentration decreases and the state of hyponatremia (Na<135 mol/l) and hypoosmolality (<270 mOsm/kg_{H2O}) develops.

Na^+ >145 mmol/l
P_{Osm} >295 mOsm/kg_{H2O}

Water depletion leads to relative excess of sodium. Its concentration rises and the state of hypernatremia (Na^+>145 mmol/l) and hyper-osmolality (P_{Osm} >295 mOsm/kg_{H2O})develops.

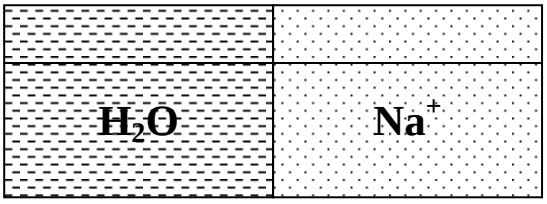
Disorders of sodium balance

Disorders of sodium balance are reflected in changes of extracellular fluid (ECF) volume



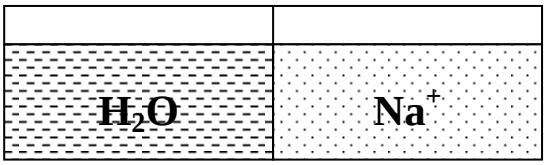
ECF – Normal

Normally there is such an amount of sodium in the organism that ECF volume is normal mans a patient is euvolemic



ECF - Expanded

When sodium is retained in the organism (water is also retained concomitantly) the ECF volume rises and oedema develops.



ECF – Decreased

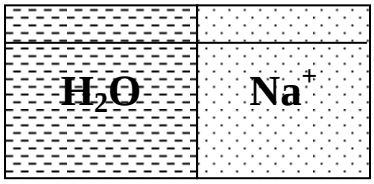
When sodium is lost from the organism (concomitantly with water) the ECF volume decreases and hypovolemia develops.

Clinical manifestation of water-sodium balance disorders

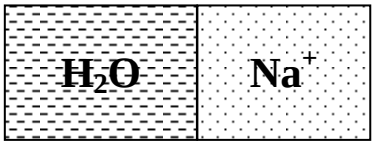
Symptoms of hypernatremia	Symptoms of hyponatremia
Disorientation	Weakness
Lethargy that progress to coma	Hyporeflexia or hyperreflexia
Increased deep tendon reflexes	Anorexia
Muscle weakness	Muscular twitches
Muscle rigidity	Exhaustion
Tremor	General rigidity
Myoclonus	Headache
Convulsions	Convulsions
	Disorientation
	Nausea
	Lethargy
	Vomiting
	Confusion
	Light-headedness

Low extracellular fluid (ECF) volume (hypovolemia)	Expanded extracellular fluid volume (overhydration)
Dry mucous membranes	Neck vein distention
Decreased skin turgor	Increased central venous pressure
Soft and contracted eyes	Edema
Flattened neck veins	Ascites
Low blood pressure	Congestive heart failure
Postural changes in blood pressure	Basal crepitations
Increased heart rate	
Low central venous pressure	
Dry shrunken tongue with deep furrows	

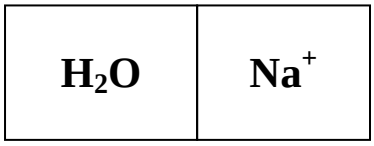
Normonatremia with expanded ECF



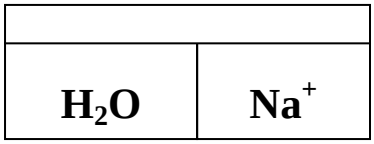
Expanded ECF



Na^+ 135 – 145 mmol/l
P_{Osm} 285 – 295 mOsm/kg_{H2O}



Normal ECF



Decreased ECF

Na^+ and water is retained in the organism, but both substances are gained proportionally so the sodium concentration and plasma osmolality doesn't change. Retention of sodium and water in the ECF leads to cardinal manifestation of the disorder – oedema.

The most common causes (clinical history):

- Congestive heart failure
- Cirrhosis of the liver
- Nephrotic syndrome
- Administration of Na^+ containing isotonic fluids (in excess)

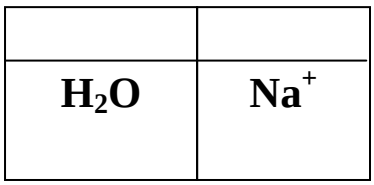
Clinical manifestation (physical examination):

- Symptoms of expanded ECF (see above)
- Symptoms of underlying disorder

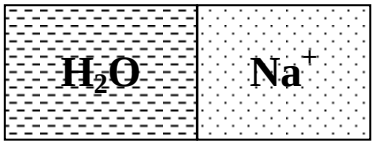
Laboratory tests:

- Blood: Plasma sodium concentration, plasma osmolality, BUN, plasma creatinine concentration, CBC.
  (Other specific for the underlying disease)
- Urine: Urine sodium concentration, urine osmolality, urine output.

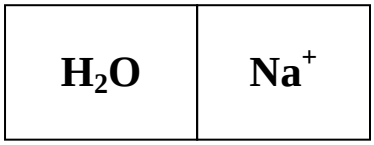
Normonatremia with decreased ECF



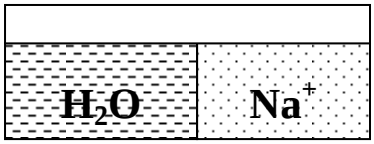
Expanded ECF



Na^+ 135 – 145 mmol/l
P_{Osm} 285 – 295 mOsm/kg_{H2O}



Normal ECF



Decreased ECF

Na^+ is lost from the organism with an isotonic fluid so there is no alteration in the plasma osmolality but ECF volume decreases and hypovolemia develops.

The most common causes (clinical history):

- Bleeding
- Diarrhea

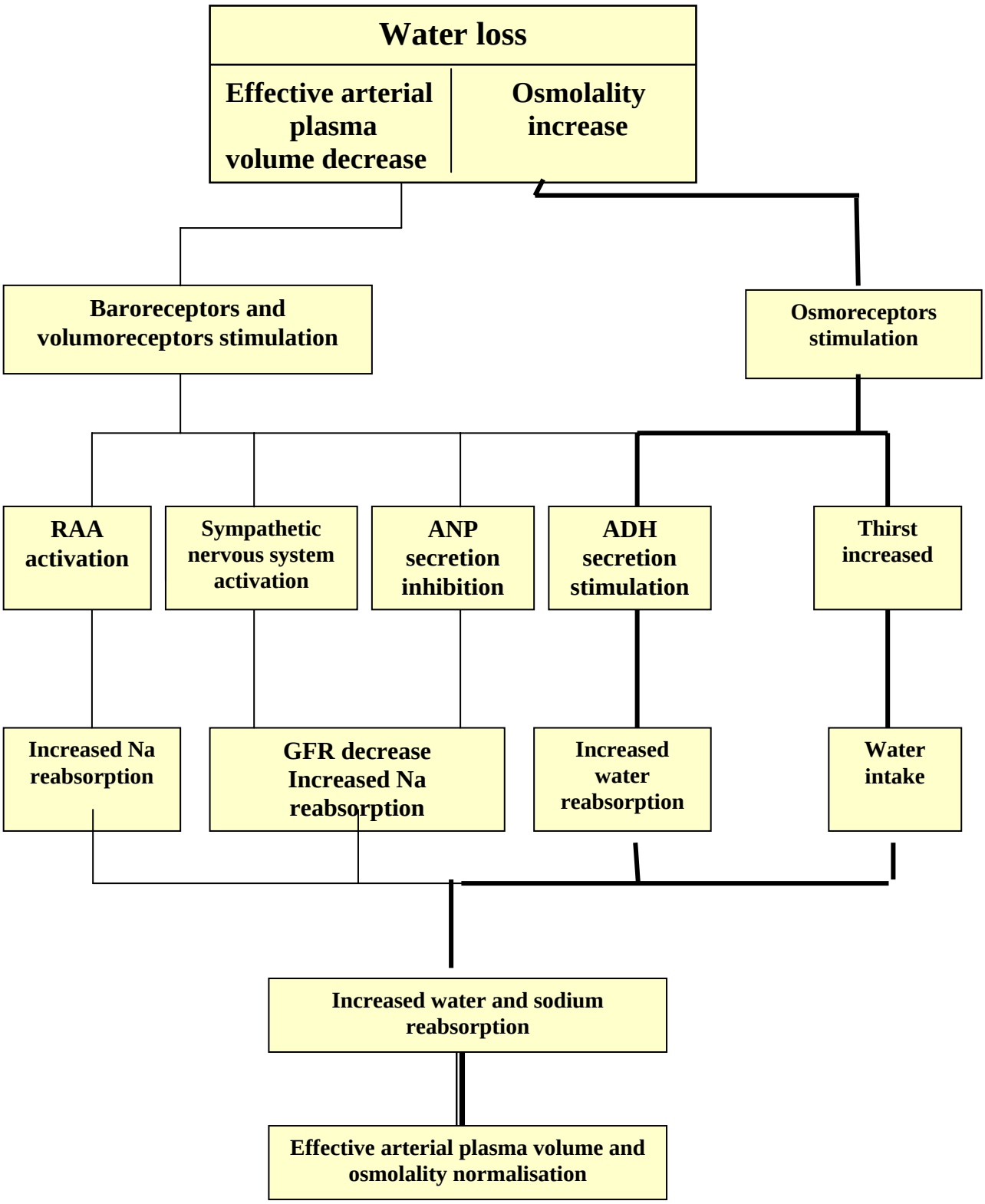
Clinical manifestation (physical examination):

- Symptoms of underlying disorder
- Symptoms of hypovolemia

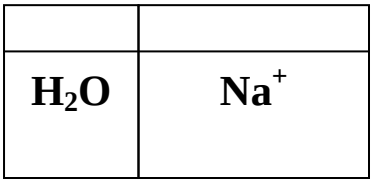
Laboratory tests:

- Blood: Plasma sodium concentration, plasma osmolality, BUN, plasma creatinine concentration, CBC.
  (Other specific for the underlying disease)
- Urine: Urine sodium concentration, urine osmolality, urine output.

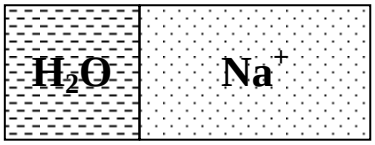
Regulation of plasma osmolality – hyperosmolality caused by water loss



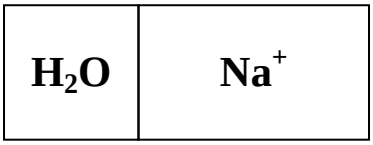
Hypernatremia with decreased ECF



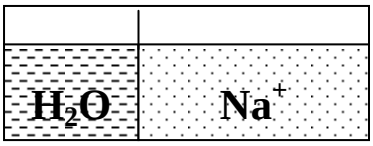
Expanded ECF



Na^+ >145 mmol/l
P_{Osm} > 295 mOsm/kg_{H2O}



Normal ECF



Decreased ECF

Water and sodium is lost as a hypotonic fluid. Relatively more water than sodium is lost resulting in the rise of the sodium concentration.

The most common causes (clinical history):

- extrarenal water loss
  - osmotic diarrheas (induced by lactulose, sorbitol, malabsorption of carbohydrate), vomiting, sweating, burns
- renal water loss
  - osmotic diuresis (glucose, mannitol, urea), diuretics

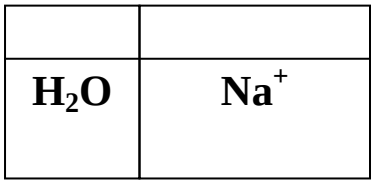
Clinical manifestation (physical examination):

- Symptoms of the underlying disorder
- Symptoms of hypovolemia
- Symptoms of hypernatremia

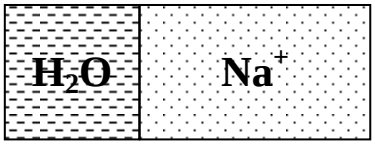
Laboratory tests:

- Blood: Plasma sodium concentration, plasma osmolality, BUN, plasma creatinine concentration, Ht, plasma protein concentration.
  (Other specific for the underlying disease)
- Urine: Urine sodium concentration, urine osmolality, urine output.

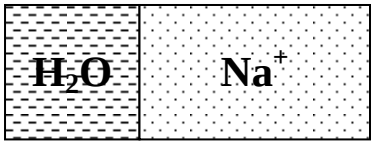
Hypernatremia with normal ECF



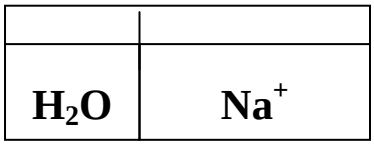
Expanded ECF



Na^+ > 145 mmol/l
P_{Osm} > 295 mOsm/kg_{H2O}



Normal ECF



Decreased ECF

Water is lost from the organism as "pure" water without or with only a small amount of electrolytes, that is why a state of relative excess of Na^+ develops and its concentration rises. As water flow continuously from cells to the ECF because of osmotic gradient, ECF volume is not decreased for the very long time and the symptoms of hypovolemia are not present.

The most common causes (clinical history):

- extrarenal water loss
  - increased insensible water loss (fever, hot and dry environment, thyrotoxicosis, hyperventilation)
- renal water loss
  - central or nephrogenic diabetes insipidus

Note: certain believe that there are examples of a state with low ECF because of the fact that dehydration may develop. In fact hypovolemia and dehydration always develops in that case if only a patient doesn't intake sufficient amount of fluid which match the water loss.

Clinical manifestation (physical examination):

- Symptoms of hypernatremia (usually mild)

Laboratory tests:

- Blood: Plasma sodium concentration, plasma osmolality, BUN, plasma creatinine concentration, Ht, plasma protein concentration.
  (Other specific for the underlying disease)
- Urine: Urine sodium concentration, urine osmolality, urine output.

The most common causes of diabetes insipidus

Causes of hypothalamic diabetes insipidus

Head trauma
Postsurgical (hypophysectomy)
Tumors
    Craniopharyngioma, pinealoma, meningioma, germinoma, glioma
    benign cysts, leukemia/lymphoma, metastatic tumors
Infections
    Tuberculosis, syphilis, mycoses, toxoplasmosis, encephalitis, basilar meningitis
Granulomatous diseases
    Sarcoidosis, histiocytosis X/ eosinophylic granuloma, Wegener's disease
Cerebrovascular disease
    Aneurysms, cavernous sinus thrombosis, postpartum pituitary infarction (Sheehan's syndrome), cerebrovascular accident
Idiopathic
    Sporadic, familial

Causes of nephrogenic diabetes insipidus

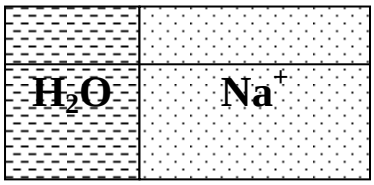
Congenital

Vassopressin V_2 – receptor mutations, aquaporin –2 water channel mutations

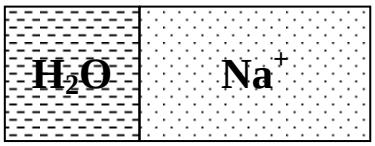
Acquired

Medications
    Lithium, Amphotericin B, Demeclocycline, Methoxyflurane
Obstructive uropathy
Chronic tubulointerstitial diseases
    Analgesic abuse nephropathy, sickle cell nephropathy, multiple myeloma, amyloidosis, sarcoidosis, Sjogren's syndrome. Policystic kidney disease, medullary cystic disease
Electrolyte diseorders
    Hypercalcemia, potassium depletion

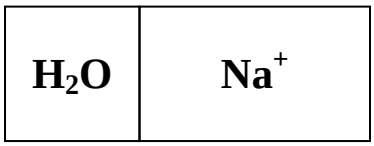
Hypernatremia with expanded ECF



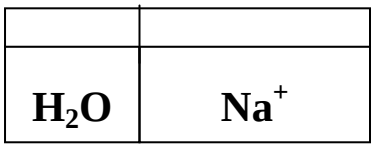
Expanded ECF



Na^+ > 145 mmol/l
P_{Osm} > 295 mOsm/kg_{H2O}



Normal ECF



Decreased ECF

The most common causes (clinical history):

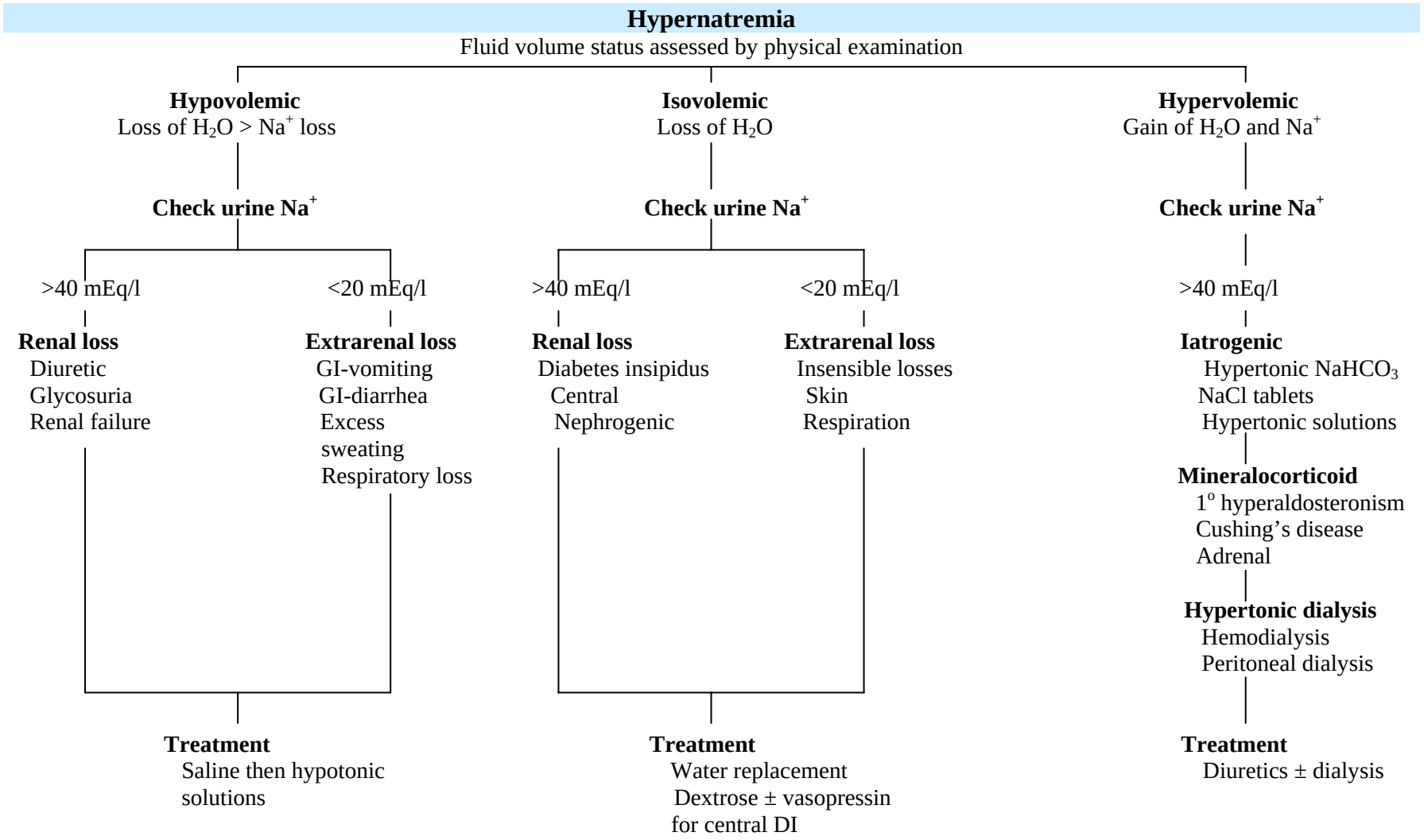
- Administration of concentrated sodium solutions e.g. concentrated sodium bicarbonate
- Ingestion of see water
- Salt inadvertently used instead of sugar

Clinical manifestation (physical examination):

- Symptoms of hypernatremia
- Symptoms of hypervolemia– central (pulmonary) oedema. *Hyperosmolality causes water flow from the interstitial space that is why circulating blood volume rises leading to congestive heart failure.*

Laboratory tests:

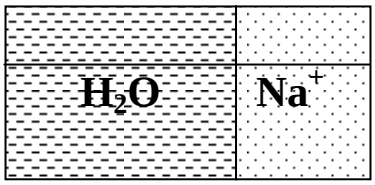
- Blood: Plasma sodium concentration, plasma osmolality, BUN, plasma creatinine concentration, Ht, plasma protein concentration.
  (Other specific for the underlying disease)
- Urine: Urine sodium concentration, urine osmolality, urine output.


Hypernatremia
Fluid volume status assessed by physical examination
Hypovolemic
Loss of H2O > Na+ loss
Isovolemic
Loss of H2O
Hypervolemic
Gain of H2O and Na+
Check urine Na+
Check urine Na+
Check urine Na+
>40 mEq/l
<20 mEq/l
>40 mEq/l
<20 mEq/l
>40 mEq/l
Renal loss
Diuretic
Glycosuria
Renal failure
Extrarenal loss
GI-vomiting
GI-diarrhea
Excess sweating
Respiratory loss
Renal loss
Diabetes insipidus
Central
Nephrogenic
Extrarenal loss
Insensible losses
Skin
Respiration
Iatrogenic
Hypertonic NaHCO3
NaCl tablets
Hypertonic solutions
Mineralocorticoid
1o hyperaldosteronism
Cushing's disease
Adrenal
Hypertonic dialysis
Hemodialysis
Peritoneal dialysis
Treatment
Saline then hypotonic solutions
Treatment
Water replacement
Dextrose ± vasopressin
for central DI
Treatment
Diuretics ± dialysis

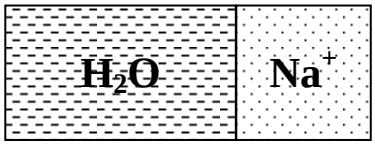
Principles of treatment of hypernatremia

1. Free water deficit = 0.5 x body weight x [(plasma sodium/140) – 1]
2. In acute hypernatremia, the water deficit can be replaced relatively rapidly. One half of the calculated water deficit can be replaced during the first 12 hours (plasma sodium concentration should than decrease by 1 to 2 mmol/l/h), and then the rate of correction slowed so that the sodium is normalized over the ensuing 24 to 48 h.
3. Although no definitive trials have been performed, in the case of chronic hypernatremia, observations suggest that the maximum safe rate at which the plasma sodium concentration should be lowered is 0.5 mmol/l per hour or 12 mmol/l per day.
4. In addition to replacing the calculated water deficit, ongoing fluid losses and basal requirements must also be replaced. If possible the cause of the increased losses should be addressed.
5. Free water can be given orally or intravenously (as dextrose in water) to patients with hypernatremia due to pure water loss.
6. An infusion of quarter-isotonic saline is preferable if Na^+ depletion is also present as typically occurs with concurrent vomiting, diarrhea or diuretic use.
7. When using glucose containing solutions, the glucose level should be monitored because hyperglycemia worsens to hyperosmolality and can lead to osmotic diuresis.
8. Deterioration in neurologic symptoms after initial improvement suggests the development of cerebral oedema and requires temporary discontinuation of water replacement.
9. In patients with volume depletion, therapy should aim first at restoring intravascular volume and then at correcting the water deficit. (Normal saline, plasma, whole blood or other volume expanders may be used)
10. In patients with hypernatremia secondary to solute administration, the hypernatremia is acute and can be rapidly corrected. These patients usually are volume overloaded and require both water administration and solute removal. A loop diuretic can be administered along with water to facilitate sodium excretion.
11. In patients with massive volume overload or renal failure, dialysis may be necessary.

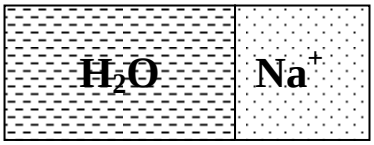
Disorders of water-sodium balance present with hyponatremia



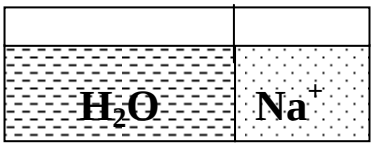
Expanded ECF



$Na^+ < 135$ mmol/l
$P_{Osm} < 285$ mOsm/kg_{H2O}



Normal ECF



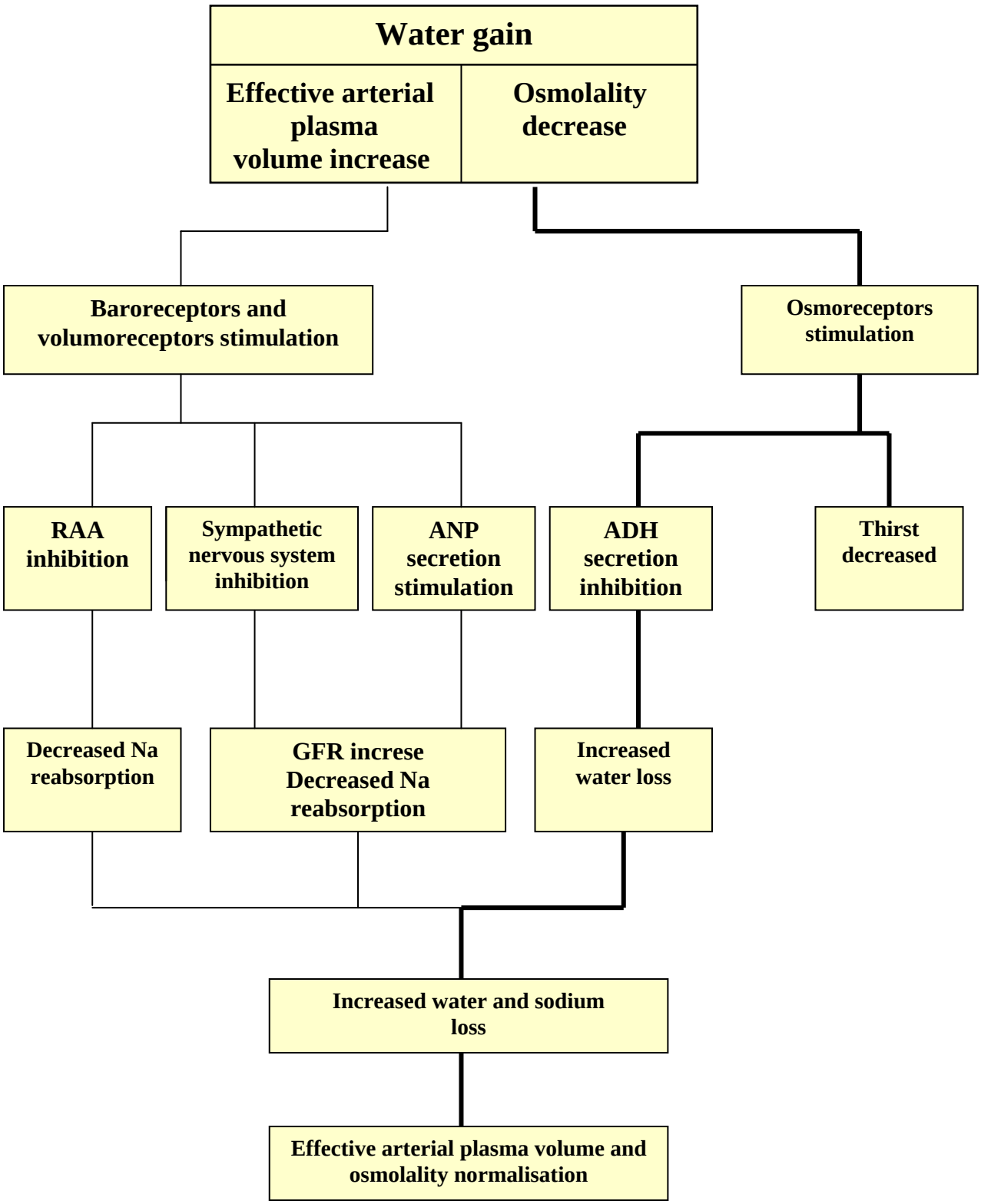
Decreased ECF

Hyponatremia and hypoosmolality develops as a result of water retention in the organism.

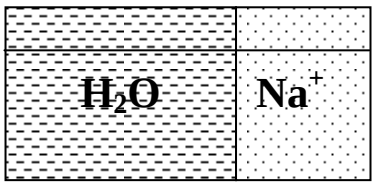
Note: the state of hypoosmolality and hyponatremia usually does not develop until two conditions are meet:

1. **water intake**
2. **excess of ADH (which unable water excess to be excreted)**

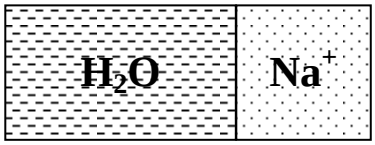
Regulation of plasma osmolality – hypoosmolality caused by water retention



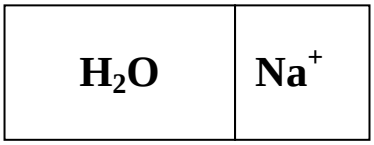
Hyponatremia and expanded ECF



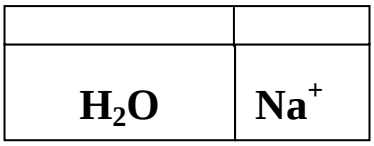
Expanded ECF



$Na^+ < 135$ mmol/l
$P_{Osm} < 285$ mOsm/kg_{H2O}



Normal ECF



Decreased ECF

Water and sodium is retained (because of underlying disease), but relatively more water than sodium is gained. ECF volume rises as a result of sodium retention, but its concentration decreases as a result of retention of water.

The most common causes (clinical history):

- Congestive heart failure
- Cirrhosis of the liver
- Nephrotic syndrome

Note: in the patients with one of that disease oedema is usually present but Na^+ concentration is usually normal. The factor responsible for the development of oedema is low ejection fraction (EF) in congestive heart failure and hypoproteinemia in patients with liver and kidney diseases – the disorders leading to low effective circulating blood volume which is a stimulus for ADH secretion. ADH is released but the amount of water retained in the circulation is too low to cause hyponatremia. When the underlying disorder begun more severe decrease of EF or further decrease of protein concentration may lead to enhanced secretion of ADH resulting in water retention and hyponatremia.

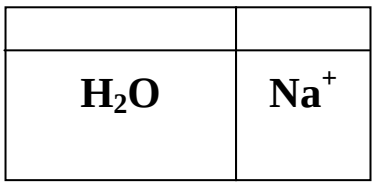
Clinical manifestation (physical examination):

- Symptoms of the underlying disease
- Symptoms of hypervolemia
- Symptoms of hyponatremia

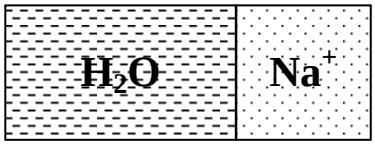
Laboratory tests:

- Blood: Plasma sodium concentration, plasma osmolality, BUN, plasma creatinine concentration, Ht, plasma protein concentration.
  (Other specific for the underlying disease)
- Urine: Urine sodium concentration, urine osmolality, urine output.

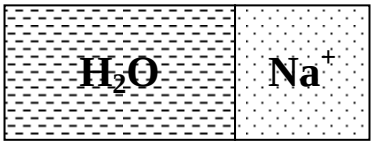
Hyponatremia with normal ECF



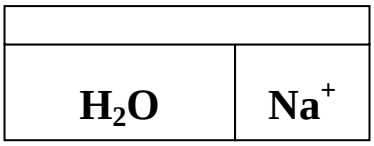
Expanded ECF



$Na^+ < 135$ mmol/l
$P_{Osm} < 285$ mOsm/kg_{H2O}



Normal ECF



Decreased ECF

Water is retained in the amount sufficient to cause Na^+ concentration decrease but ECF volume doesn't rise because sodium metabolism is not altered. Sodium is excreted properly via the kidney, is not retained in the organism that is why clinically important oedema doesn't develop.
As hyponatremia in that situation is usually not severe patients are asymptomatic until enhanced water ingestion or administration take place. As ADH is in excess and water can't be excreted, acute water intoxication may develop.

The most common causes (clinical history):

- **Acute hyponatremia (Acute water intoxication) – rapid administration of water plus**
  - Acute hypovolemia (e.g. haemorrhage)
  - During early postoperative period
  - During labour and delivery
  - Schizophrenia
  - In the presence of a chronic cause of impaired water exertion (see below)
- **Chronic hyponatremia**
  - Primary polydipsia
  - Decreased solute intake (beer potomania)
  - Antidiuretic drug administration
  - Syndrome of inappropriate AVP secretion (SIADH)
  - AVP release due to pain, nausea, drugs
  - Glucocorticoid deficiency
  - Anterior hypopituarism
  - Abrupt withdrawal of glucocorticoid drug therapy
  - Severe hypothyroidism
  - Chronic renal insufficiency

Clinical manifestation (physical examination):

- Symptoms of the underlying disorder (if present)
- Symptoms of hyponatremia

Symptoms of acute hyponatremia

Mild hyponatremia (sodium > 125 mmol/L) is usually asymptomatic.

Sodium < 125 mmol/L
- weakness
- exhaustion

Sodium < 120 mmol/L
- headache
- nausea
- vomiting
- anorexia
- disorientation
- lethargy
- pathological deep tendon reflexes

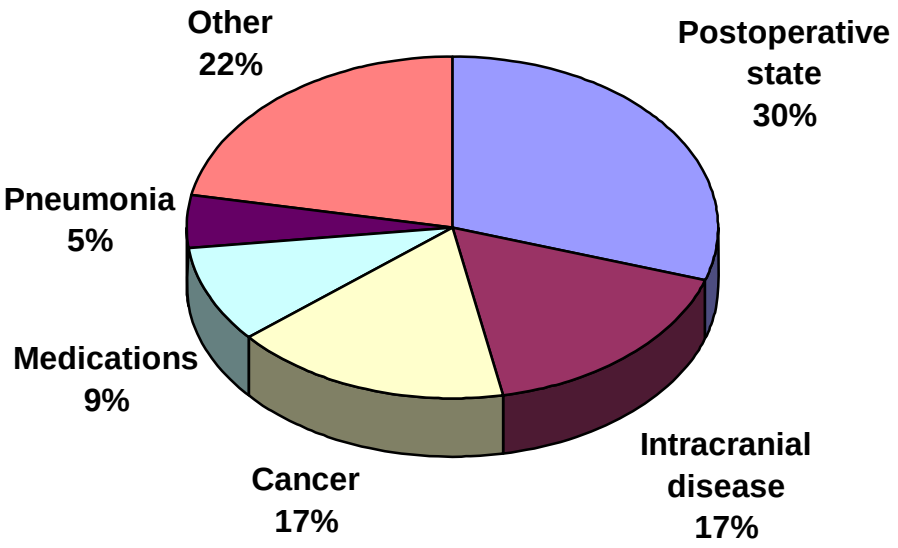
Sodium < 110 mmol/L
- papilledema and other manifestations of increased intracranial pressure
- seizures
- coma

There is a poor correlation between the severity of symptoms and the degree of chronic hyponatremia, reflecting variable degrees of brain adaptation.

Laboratory tests:

- Blood: Plasma sodium concentration, plasma osmolality, BUN, plasma creatinine concentration, CBC. *(Other specific for the underlying disease)*
- Urine: Urine sodium concentration, urine output, urine osmolality.

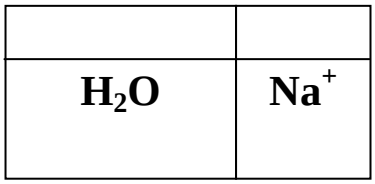
SIADH



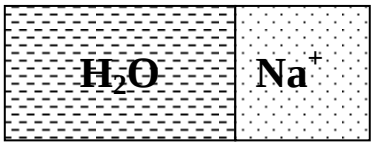
Diagnostic criteria:

1. Hypotonic hyponatremia
2. Urine osmolality greater than 100 mOsm/kg_{H2O}
3. Urine sodium concentration greater than 40 mmol/l *(unless the patient is volume depleted for some other reason)*
4. Absence of extracellular volume depletion or expansion
5. Normal thyroid and adrenal function
6. Normal cardiac, hepatic and renal function

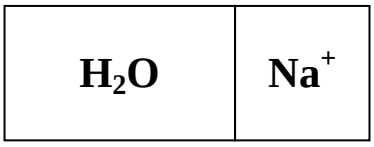
Hyponatremia with low ECF



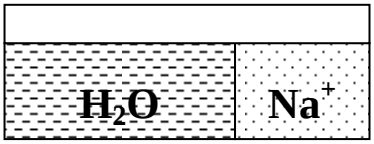
Expanded ECF



$Na^+ < 135$ mmol/l
$P_{Osm} < 285$ mOsm/kg_{H2O}



Normal ECF



Decreased ECF

That state is usually the result of improper treatment of hypovolemia present with normal or low osmolality. When a patient is loosing isotonic or hypotonic fluid is loosing water and electrolytes. When fluid losses are replaced only with nonelectrolytes fluids (dextrose solutions) than most water load flows into the cells, with only 1/3 left in the ECF. Administrations of pure water cause decrease of sodium concentration but usually doesn't cause the restoration of the ECF volume that is why hypovolemia is still present.

The most common causes (clinical history):

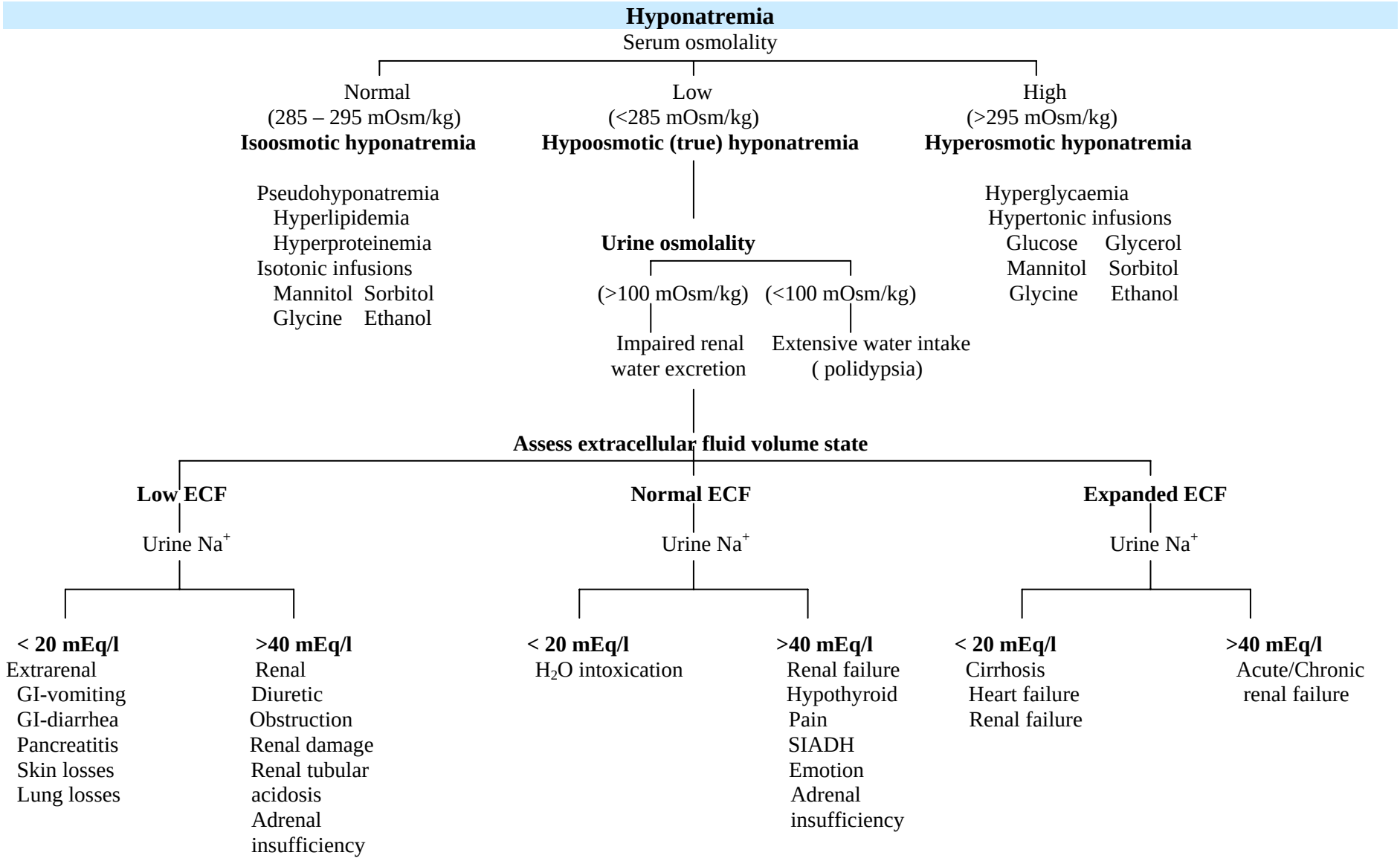
- Extensive sweating, burns
- Gastrointestinal loss: vomiting, tube drainage, fistula, obstruction, diarrhoea
- Renal loss: diuretics, osmotic diuresis, hypoaldosteronism, salt-wasting nephropathy, postobstructive diuresis

Clinical manifestation (physical examination):

- Symptoms of underlying disorder
- Symptoms of hypovolemia (usually mild)
- Symptoms of hyponatremia (usually mild)

Laboratory tests:

- Blood: Plasma sodium concentration, plasma osmolality, BUN, plasma creatinine concentration, Ht, plasma protein concentration.
  (Other specific for the underlying disease)
- Urine: Urine sodium concentration, urine osmolality, urine output.


Hyponatremia
Serum osmolality
Normal
(285 – 295 mOsm/kg)
Isoosmotic hyponatremia
Low
(<285 mOsm/kg)
Hypoosmotic (true) hyponatremia
High
(>295 mOsm/kg)
Hyperosmotic hyponatremia
Pseudohyponatremia
Hyperlipidemia
Hyperproteinemia
Isotonic infusions
Mannitol Sorbitol
Glycine Ethanol
Urine osmolality
(>100 mOsm/kg)
(<100 mOsm/kg)
Impaired renal water excretion
Extensive water intake (polidypsia)
Hyperglycaemia
Hypertonic infusions
Glucose Glycerol
Mannitol Sorbitol
Glycine Ethanol
Assess extracellular fluid volume state
Low ECF
Normal ECF
Expanded ECF
Urine Na+
Urine Na+
Urine Na+
< 20 mEq/l
Extrarenal
GI-vomiting
GI-diarrhea
Pancreatitis
Skin losses
Lung losses
>40 mEq/l
Renal
Diuretic
Obstruction
Renal damage
Renal tubular acidosis
Adrenal insufficiency
< 20 mEq/l
H2O intoxication
>40 mEq/l
Renal failure
Hypothyroid
Pain
SIADH
Emotion
Adrenal insufficiency
< 20 mEq/l
Cirrhosis
Heart failure
Renal failure
>40 mEq/l
Acute/Chronic renal failure

Principles of treatment of severe hypotonic hyponatremia
(Sodium < 120 mmol/L)

Acute	- with hypovolemia	0.9% NaCl, rapid correction 1 – 2 mmol/L/h during the first 6-8 hours, subsequently 0.5 mmol/L/h
	-with euvolemia	3% NaCl, rapid correction 1 – 2 mmol/L/h during the first 12 hours subsequenly 0.5 mmol/L/h furosemide (monitoring of the serum sodium concentration hourly)
	-with oedema	hemodialisis with ultrafiltration or hemofiltration
Chronic	-with hypovolemia	0.9% NaCl, slow correction 0.5 mmol/L/h, potassium supplementation
	-with euvolemia	water restriction SIADH – demeclocycline potassium supplementation
	-with oedema	water and sodium restriction furosemide angiotensin converting enzyme inhibitors potassium supplementation

- *Acute hyponatremia* – symptomatic
- *Chronic hyponatremia* – asymptomatic

1. Asymptomatic or ≥ 120 mmol/l hyponatremia doesn't require aggressive treatment.
2. In acute hyponatremia sodium rise during the first 24-h should be less than 20 mmol/L (optimally 10-12 mmol/24 h).
3. In chronic hyponatremia sodium rise during the first 24-h should be no more than 10-12 mmol/L.
4. Desired sodium concentration during the first 24 h is 120-125 mmol/L (no 140 mmol/L). Sodium deficit = 0.6 x body weight x (125 – P_{Na})
5. When sodium concentration is restored to 120-125 mmol/L further normalization should be achieved during the next few days via fluid restriction.

Causes of Hypokalemia

Decreased intake

Starvation
Clay ingestion

Redistribution into cells

Metabolic alkalosis
Insulin administration
Beta2 adrenergic agonists (endogenous or exogenous)
Alpha-adrenergic antagonists
Vitamin B12 or folic acid (red blood cell production)
Granulocyte-macrophage colony stimulating factor (white blood cell production)

Increased loss

Nonrenal

Gastrointestinal loss (diarrhea, vomiting)
Integumentary loss (sweat)

Renal

Increased distal flow: diuretics, osmotic diuresis, salt-wasting nephropathies
Increased secretion of potassium

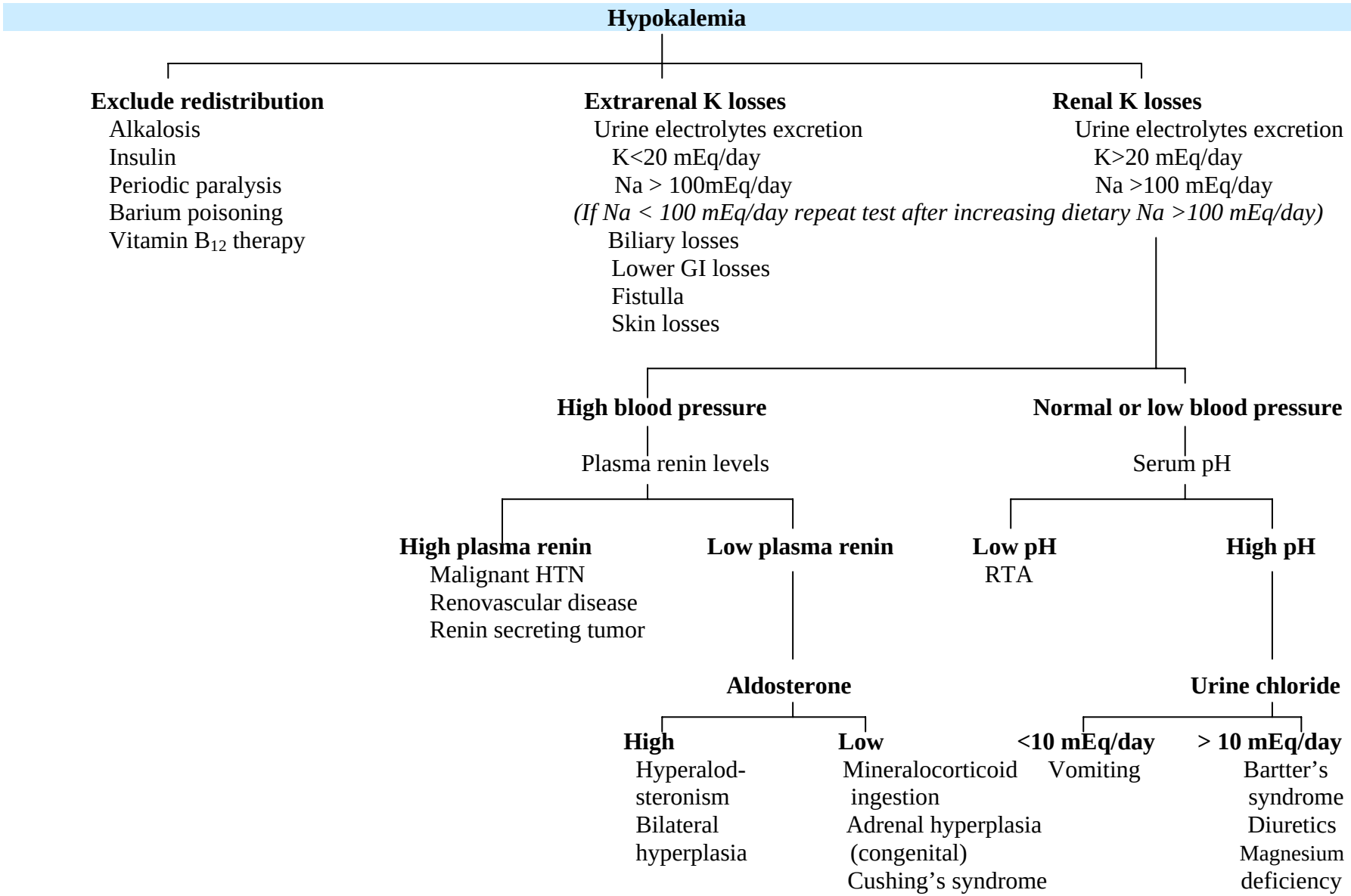
Mineralocoricoid excess: primary hyperaldosteronism, secondary hyperaldosteronism

Symptoms of hypokalemia

Physical examination	ECG changes
• Muscle weakness • Muscle cramps • Paresthesias • Muscular pains • Lethargy • Drowsiness • Confusion • Irritability • Postural hypotension • Anorexia • Nausea to vomiting • Abdominal cramps	• Depression of the ST segment • Lowering, flattening, or inversion of the T wave • Presence of an elevated U wave • Increase in P-wave amplitude • Prolongation of PR interval • Severe hypokalemia may prolong the QRS period by 0.1 to 0.3s., without changes in QRS configuration • Arrhythmias

Laboratory tests:

- Blood: Plasma potassium concentration, plasma osmolality, BUN, plasma creatinine concentration
  (Other specific for the underlying disease)
- Urine: Urine potassium excretion, urine output, urine osmolality.


Hypokalemia
Exclude redistribution
Alkalosis
Insulin
Periodic paralysis
Barium poisoning
Vitamin B12 therapy
Extrarenal K losses
Urine electrolytes excretion
K<20 mEq/day
Na > 100mEq/day
(If Na < 100 mEq/day repeat test after increasing dietary Na >100 mEq/day)
Biliary losses
Lower GI losses
Fistulla
Skin losses
Renal K losses
Urine electrolytes excretion
K>20 mEq/day
Na >100 mEq/day
High blood pressure
Normal or low blood pressure
Plasma renin levels
Serum pH
High plasma renin
Malignant HTN
Renovascular disease
Renin secreting tumor
Low plasma renin
Low pH
RTA
High pH
Aldosterone
Urine chloride
High
Hyperalod-steronism
Bilateral hyperplasia
Low
Mineralocorticoid ingestion
Adrenal hyperplasia (congenital)
Cushing's syndrome
<10 mEq/day
Vomiting
> 10 mEq/day
Bartter's syndrome
Diuretics
Magnesium deficiency

Principles of potassium supplementation

1. The quantity of potassium for intravenous therapy may be difficult to ascertain because serum potassium may not reflect total body potassium.

2. A decrement of 1 mmol/L in the plasma potassium concentration (from 4.0 t0 3.0 mmol/L) may represent a total body K deficit of 200 to 400 mmol, and patients with plasma levels under 3.0 mmol/L often require in excess of 600 mmol of K to correct the deficit.

- if the serum potassium is less than 3 mEq/l, an infusion of 200 to 400 mEq of potassium is generally necessary to raise the serum K by 1 mEq/L
- if serum potassium is between 3 and 4.5 mEq/L an infusion of 100-200 mEq/l will raise the serum potassium by 1 mEq/L.

3. The maximum concentration of administered K should be no more than 40 mEq/L via a peripheral vein or 60 mEq/L via a central vein.

4. The rate of infusion should not exceed 20 mEq/h.

    - If there are indications for urgent therapy, such as serum potassium less than 2.0 mEq/L, abnormal electrocardiogram, or paralysis, potassium may be infused at rates up to 40 mEq/h in concentrations not greater than 60 mEq/L. Up to 400 mEq KCl may be administered i.v. per day.

    - When plasma potassium concentration reaches 2.5 meq/L, the rate of administration should be slowed to 10 mEq/h, and solutions should contain no more than 30 mEq/L.

    - If serum potassium is greater than 2.5 mEq/l and the electrocardiographic disturbances of hypokalemia are absent, potassium should not be administered at rates greater than 10 mEq/h or in concentrations above 30 mEq/L. Not more than 100 to 200 mEq/day should be given.

5. Whenever potassium is infused, it must first be determined that the patient is not hyperkalemic or oliguric, and adequacy of renal function should be established (e.g., by serum creatinine levels)

6. If the patient receives potassium at rates of 120 mEq/day or 20 mEq/h for more than 2h, the ECG should be monitored continuously and the serum potassium measured with each 50-100 mEq infused.

7. With severe hypokalemia, potassium should be infused in saline if there are no contraindications rather than in dextrose and water because infusion of glucose may further depress the serum potassium.

8. Potassium should never be infused as a bolus.

9. When potassium is added to an intravenous container, particularly a plastic nonrigid one, it may not mix well; and during intravenous administration it may enter the blood stream as a bolus and cause potassium intoxication. Better mixing is obtained by administering potassium directly into the container rather than into the injection port. Also, instilling the potassium before the container is inverted seems to promote mixing.

Causes of hyperkalemia

I. **Increased intake** (usually in patients with renal failure)

II. Redistribution out of cells

1. Metabolic acidosis
2. Insulin deficiency
3. Hyperosmolality (usually hyperglycaemia)
4. Beta2 adrenergic antagonists
5. Alpha-adrenergic antagonists
6. Cell damage (lysis)

III. Decreased potassium secretion

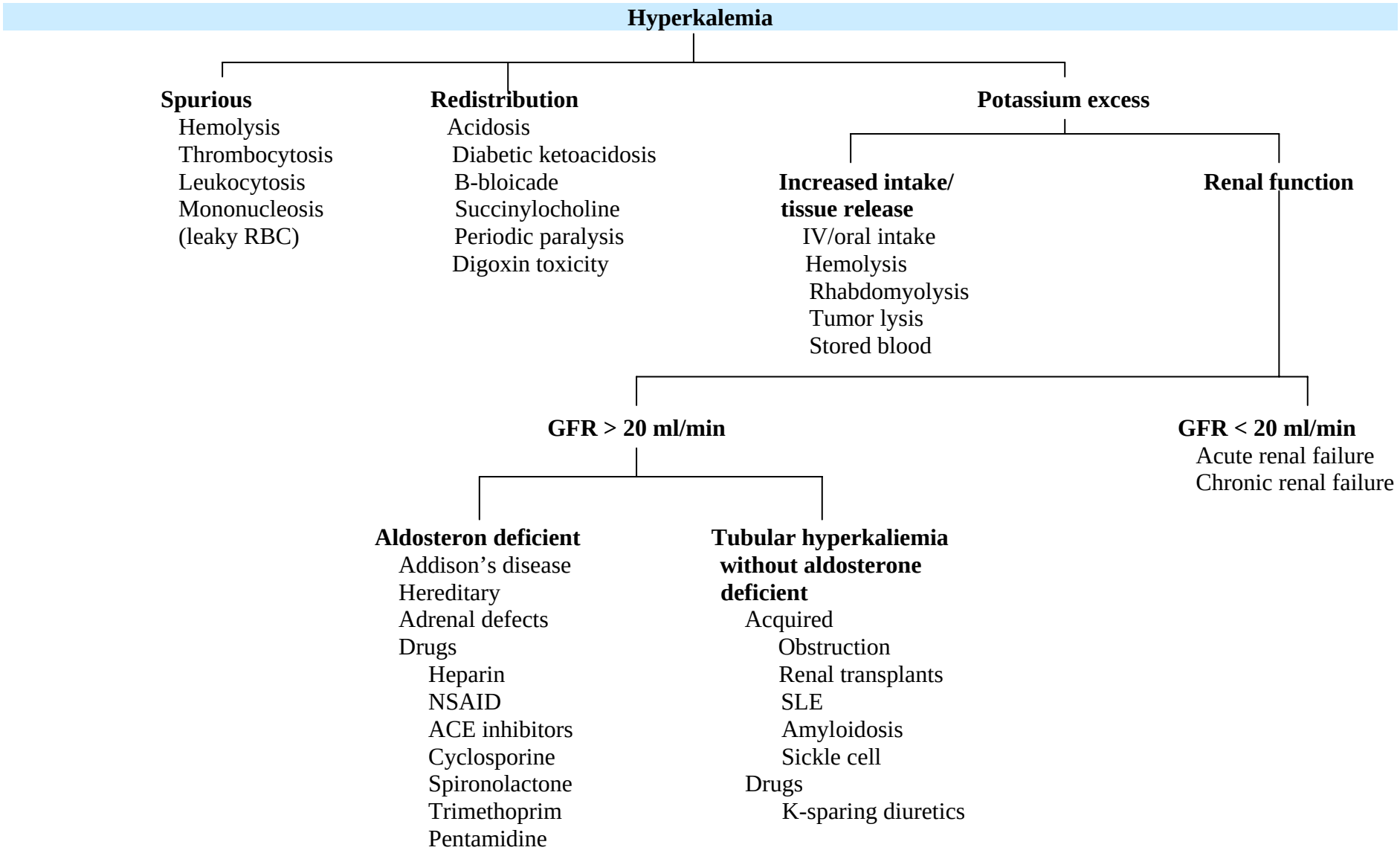
1. Renal failure
2. Primary hypoaldosteronism: adrenal insufficiency, adrenal enzyme deficiency
3. Secondary hypoaldosteronism: hyporeninemia, drugs ACE inhibitors, NSAIDs)
4. Resistance to aldosterone: pseudohypoaldosteronism, tubulointestitial disease, drugs (K-sparing diuretics)

Symptoms of hyperkalemia

Physical examination	ECG changes
• Usually asymptomatic • Muscular weakness • Tremor • Paresthesias	• Peaked T waves • Prolonged PR interval • Disappearance of the P waves • Prolongation and decomposition of the QRS complex • Ventricular fibrillation

Laboratory tests:

- Blood: Plasma potassium concentration, plasma osmolality, BUN, plasma creatinine concentration *(Other specific for the underlying disease)*
- Urine: Urine potassium excretion, urine output, urine osmolality.


Hyperkalemia
Spurious
Hemolysis
Thrombocytosis
Leukocytosis
Mononucleosis
(leaky RBC)
Redistribution
Acidosis
Diabetic ketoacidosis
B-bloicade
Succinylocholine
Periodic paralysis
Digoxin toxicity
Potassium excess
Increased intake/ tissue release
IV/oral intake
Hemolysis
Rhabdomyolysis
Tumor lysis
Stored blood
Renal function
GFR > 20 ml/min
GFR < 20 ml/min
Acute renal failure
Chronic renal failure
Aldosteron deficient
Addison's disease
Hereditary
Adrenal defects
Drugs
Heparin
NSAID
ACE inhibitors
Cyclosporine
Spironolactone
Trimethoprim
Pentamidine
Tubular hyperkaliemia without aldosterone deficient
Acquired
Obstruction
Renal transplants
SLE
Amyloidosis
Sickle cell
Drugs
K-sparing diuretics

References:

1. B.D. Rose: *Clinical physiology of acid-base and electrolyte disorders*. McGraw-Hill Health Professions Division 2001
2. Harrison's Principles of Internal Medicine. 14th ed. McGraw-Hill. 1998.
3. Henry J.B. Clinical Diagnosis and Management by Laboratory Methods. 19th ed. W.B. Saunders Company. Philadelphia 1996.
4. Ravel R. Clinical Laboratory Medicine. Clinical Application of Laboratory Data. 6th ed. Mosby-Year Book. 1995.

Biochemical effects of neoplastic diseases

Miłosława Zowczak-Drabarczyk MD

Process of generation of different tumor markers:

Cancer cell

↓ ↓

rapid cell proliferation **dedifferentiation**

↓ ↓

increase in concentration of normal proteins and metabolites

elevated levels of carcinoembryonic proteins and production of ectopic tumor markers

CLASSICAL TUMOR MARKERS:

GI cancers, especially colorectal cancer	CEA
gastric and pancreatic cancer	CA 19-9
Hepatocellular carcinoma, testicular cancer	AFP
choriocarcinoma, testicular cancer	β- hCG
breast cancer	CaA15-3
ovarian cancer	CA 125
prostate cancer	PSA

Carcinoembryonic antigen (CEA)

- a glycoprotein still the most widely used as an tumor marker for **GI cancer** today.
- to **follow** patients with colorectal cancer **during therapy** and to **detect recurrence**.
- **minimal transient CEA elevations** can be influenced by smoking history, chronic bronchitis, hepatitis, cirrhosis, pancreatitis, gastritis and inflammatory bowel disease.
- **CEA is metabolized by the liver** and its damage can impair CEA clearance and lead to increased levels in the blood circulation.

Human chorionic gonadotropin (hCG)

- It is a number of glycoprotein hormone family synthesized and secreted by **trophoblast cells of the placenta**.
- a free **β-subunit of hCG** has been detected in the serum of **pregnant women** and
- in patients with: **gestational trophoblastic disease** (e.g. choriocarcinoma), **testicular carcinoma** (more than 60% of patients with nonseminomas and up to 30% with seminomas) and **rarely** in patients with **other malignancies** such as bladder cancer.

Alpha-fetoprotein (AFP)

- AFP is the major fetal serum protein and is synthesized by the yolk sac and the fetal hepatocytes, and to a lesser extent by the fetal GI and kidney.
- AFP is also one of the major carcinoembryonic proteins.
- Elevated AFP in patients with primary hepatocellular carcinoma and germ-cell tumors of testicular, extragonadal and ovarian origin.
- In both hepatomas and germ-cell tumors, the AFP lever correlates with tumor bulk and frequency of elevated AFP levels increases with disease stage.
- AFP is the most useful serum marker for the management and the diagnosis of hepatocellular carcinoma.

CA 19-9

- **Increased** levels of **CA 19-9** is found in patients with a **wide range of GI malignancies** and also in a small number of **bladder tumors**.
- Serum **CA 19-9** concentrations are highly and frequently **elevated** in both **gastric and pancreatic carcinomas** and is useful for **monitoring** the success of **therapy** and for **detecting recurrence**
- **Monitoring** the patient **after gastric cancer surgery** with both**: CEA and CA 19-9** is the **gold standard,** now

CA 125

- It is a carbohydrate antigen normally present during embryonic development of coelomic epithelium and is present in adult structures derived from it.
- **Increased** levels of **CA125** are found in **more than 80% on nonmucinous epithelial ovarian carcinomas at presentation** and **correlate with tumor bulk**. **CA125** is used for **monitoring** possible relapse and **elevated concentrations may precede clinical recurrence by months.**
- **CA 125** is also used clinically for a **follow-up on the uterine tumors and benign tumors including endometriosis.**

Prostate-specific antigen (PSA)

- PSA is synthesized in the epithelial cells of the prostate gland.
- Usefulness: helpful in diagnosis and management (particularly after surgery) of prostate cancer.
- Lack of cancer specificity and not full cancer sensitivity are the drawbacks of PSA.
- The use of digital rectal examination (or transrectal USG) in combination with PSA as a screening tool for detecting clinically significant prostate cancer was previously recommended

Methods to improve PSA clinical utility:

→ **age-specific** reference ranges,

→ **free** and **complexed PSA**.

Methods for utilizing PSA if you have a diagnostic problem:

- ***PSA velocity,***
- ***PSA density.***

CA 15-3

- It is a number of carbohydrate antigens useful in **the management of breast cancer** patients.
- Levels of **Ca 15-3 are raised in 20%** of women **with localized breast cancer** and up to **80 % in metastatic** disease.
- It has a **specificity of 86 % and sensitivity of 30%** and has been a **useful tool in monitoring** the course of **the disease**.
- **Ca 15-3 can rise** also **in other malignancies**, e.g.: cancer of the **stomach, pancreas, lung and uterus.**

Tissue polypeptide antigen (TPA) and tissue polypeptide-specific antigen (TPS)

- It is a mixture of **cytokeratin fragments**. Cytokeratins form the protein cytoskeleton of epithelial cells and increase in the circulation in the presence of rapid cell growth. **TPA** appears to be a **measure of cellular proliferation-reflects speed of mitosis.**
- Monoclonal mapping of **TPA** molecule has revealed many different epitopes: one of essential is **TPS**.
- In contrast to other tumor markers related rather to tumor mass, **TPA** and **TPS** are sensitive but nonspecific markers **for discriminating between progressive disease and disease in complete remission.**
- Many reports emphasize **the use of TPA, TPS in combination with other markers, especially CEA, for earlier detection and monitoring a variety of carcinomas**, including breast , colorectal, ovarian, bladder, pancreas and lung.

Molecular definition of malignant tumor

normal cell:

accumulation of genetic errors → **malignant cell:**

not under growth nor differentiation control mechanisms any more

ONCOGENES and its protein products are growth inducing.

<u>In normal cells</u> its precursors-protooncogenes:

- play important regulatory role of cell proliferation, differentiation and maturation.
- its protein products can act as growth factors, its receptors, signal transmission or transcriptional factors in nucleus

Activation of **protooncogenes** → **oncogenes** can be caused by **implanted viral gene** or **structural changes in cell genome** (point mutation, translocation, amplification of protooncogenes).

<u>Examples:</u> **ras** encodes proteins H-ras, K-ras, N-ras (pulmonary ca, ca of pancreas, GI tract ca, prostate ca, AML) →**loosing of contact inhibition**; **myc** (colorectal ca, breast ca) →**immortality**, **bcl-2**→**prevents apoptosis** p53 dependent and p53 independent.

TUMOR SUPPRESSOR GENES and its protein products are growth-inhibiting.
In normal cells play role in:

- **growth regulation**
- **DNA repair** (when cells sustain DNA damage, cellular „hibernation", manifested by an arrest at the G1 or G2 checkpoint permits repair to take place and prevents the accumulation of mutant sequences)
- apoptosis/cell survival (**promotion of apoptosis**-programmed cell death→to clear tissues of damaged cells with a high cancer potential)
- **chromosomal stability**
- **cell adhesion**
- **transcription**

  Examples: p53 (the encoding gene for p53 has been found to be **mutated in about half of almost all types of cancer**. It can be measured in ether tissue, fibroblast, white blood cell, or serum. The wild-type p53 protein in the blood circulation is not detectable due to its short half life, missense mutations increase the half life and quantity of the p53 protein. A mutant p53 renders cells less likely to undergo apoptosis after cellular stress, with chemotherapeutic agents and gamma irradiation); **BRCA1** and **BRCA2 →susceptibility to breast and ovarian ca**; **rb →retinoblastoma**.

EXAMPLES OF MOLECULAR TUMOR MARKERS/THERAPEUTIC TARGETS:

breast cancer	Estrogen receptors, HER-2
CML,	bcr/abl fusion gene (Philadelphia chromosome)
CML, GIST	tyrosine kinase
breast, lung, colon cancer	vascular endothelial growth factor
breast, ovarian cancer	BCRA 1, BCRA 2
epithelial cancers expressing CEA	antiCEA mAbs

HER-2

- HER is a proto-oncogene encoding a transmembrane receptor (EGFR) with tyrosine kinase activity.
- HER-2 has been found to be important for regulating cell growth and differentiation.
- It has been demonstrated that protein overexpresion inversely correlates with the estrogen receptor level and predicts resistance to antiestrogen therapy, even in estrogen receptor positive disease. Also it predicts worse answer to classical chth (better to taksons and antracyclins).
- Breast cancer showing HER-2 gene amplification and protein overexpression has a worse clinical prognosis.
- Also, high HER-2 expression is highly associated with androgen independence in prostate cancer and may identify patients more likely to have disease progression.
- MAbs (monoclonal antibodies) to HER-2 can inhibit the proliferation of tumor cells that overexpress this gene and mediate antibody-dependent cellular cytotoxicity. The drug is called Trastuzumab (Herceptin).

Usefulness of tumor markers

Monitoring treatment :

- is **one of the most useful applications** of TM,
- the serum level of tumor marker reflects well success of surgery or the efficacy of chemotherapy and radiotherapy,
- levels of tumor marker can be a guide for the selection of the most effective drug for each individual case (e.g. estrogen and progesterone receptors in breast cancer tissue, HER-2 in breast or prostate cancer)
- detecting elevated levels of marker after surgery may indicate incomplete removal of the tumor, the presence of metastases, or recurrence.

Detection of recurrence:

- is **the second most useful application** of tumor markers,
- the appearance of most tumor markers has a „lead time" of several months prior to the stage at which many of the physical procedures could not detect tumor,
- the specificity of tumor markers is not a problem for this application.

Prognosis:

- most tumor markers become increasingly elevated when tumor metastasized,
- the detection of tumor markers highly associated with malignancy and metastases usually suggests more aggressive treatment.

Diagnosis:

The problems with both specificity and sensitivity associated with most tumor markers precludes their measurement for their use in the diagnosis of cancer.

- the frequency of detecting elevated levels of tumor markers in
- non-neoplastic diseases discourages their use in diagnosis,
- the overlap observed between the normal concentrations and the concentrations
- of tumor marker in patients with proven cancer.

Screening:
None of the tumor markers discovered have adequate specificity and sensitivity for screening.

Exceptions:

- in South Asia and China the screening for primary hepatoma is based on the measurement of serum AFP and abdominal US,
- the feasibility of screening ovarian cancer in women by measuring serum CA 125 is still in the process of investigation,
- BCRA 1 and BCRA 2 for susceptibility of breast and ovarian cancer.

Recommendations of ordering tumor markers tests

⇒ never relay on the single test (it is difficult to differentiate between malignant diseases and either benign or non-neoplastic diseases based on the single test)

⇒ when ordering serial testing, be certain to order every test from the same laboratory using the same assay kit

⇒ be certain that the tumor marker selected for monitoring recurrence was elevated in the patient before surgery

⇒ consider the half-life time of the tumor marker when interpreting the test result

⇒ consider how the tumor marker is removed or metabolized from the blood circulation (elevated serum tumor markers are frequently detected in patients with a renal or a liver disease depending on whether the tumor marker is removed through glomerular filtration or metabolized by the liver)

⇒ consider ordering multiple tumor markers to improve both the sensitivity and specificity

⇒ be aware of the presence of ectopic tumor markers.

Breast cancer: an example of full spectrum of TM used in clinical practice:

1. **Markers of morphological differentiation**:
   - H-P type and grading
   - ER, Pg receptors in breast cancer tissue (prognostic and predictive factor: +/+ 80% positive answer of therapy , +/- or -/+ 60%, -/- 10%)
   - DNA ploide

2. **Markers of neo invasion**:
   - metaloproteinases (enzymes responsible for degradation of extracellular matrix; e.g. gelatynases, etc)
   - cathepsyn D
   - growth factors, oncogenes and its protein products (e.g. HER-2)

3. **Markers of proliferation**
   - accumulation of p53, etc.
   - TPS, TPA (sensitivity 95%)

4. **Serum markers**:
   - CEA (never used alone, for estimation of bone metastases)
   - CA 549 (sensitivity rises with advance of the disease)
   - CA 15-3 (a STANDARD!, specificity 85-100%, also to follow up!)
   - MCA
   - Ca 125 (indicator of pulmonary meta)

Notice!!!! The best constellation of tests: TPA+TPS+CA 15-3

Hemoccult II (guaiac-based) slide test for fecal occult blood

In the presence of peroxidase or pseudoperoxidase (red blood cells) in fecal specimen and with the addition of hydrogen peroxide in the test, the indicator (guaiac) is oxidized to a blue quinone compound.

Because the pseudoperoxidase activity of hemoglobin tends to be altered as it passes though the GI tract, bleeding from the upper GI is less likely to produce a positive result than is lower GI tract bleeding.

The American Cancer Society has made the following recommendations for using the Hemoccult II test:

1. Subjects should avoid ingesting red meat, fish and high peroxidase foods (horseradish, turnips, bananas, black grapes, pears, and plums)for three days before and during testing.
2. Use of vitamin C and other antioxidants, iron tablets and NSAIDs should be avoided.
3. Two samples of each of three consecutive stools should be tested
4. The delay between preparation and lab testing should not exceed six days.
5. Slides should not be dehydrated
6. A single positive smear should be considered a positive test result, even in the absence of dietary restriction.

The sensitivity of FOBT for detecting asymptomatic colorectal ca and adenomas is difficult to estimate. Between 50% and 90 % of tests in patients with known colorectal ca have been reported to yield positive results with Hemoccult II. The positive predictive value of the test in two controlled trials was reported to be 10 % for carcinoma and 30 % for adenomas for the initial screening test.

Immunochemical stool tests for human hemoglobin have a 97 % sensitivity for colorectal ca and 76 % sensitivity for adenomas of larger than 1 cm. Estimated specificity was 98%. The major advantage of the immunochemical tests is the absence of a need for dietary modification.

References

1. Perry M.C. Annual Meeting May 15-18, 1999, Atlanta, GA. 35th ed. American Society of Clinical Oncology, Educational Book, Aleksandria 1999
2. DeVita V.T., Hellman S., Rosenberg S.A. Cancer Principles & Practice of Oncology. 3rd ed. J.B. Lippnicott Company, Philadelphia 1989.
3. Cecil Essentials of Medicine. 3rd.ed. W.B. Saunders Company. Philadelphia 1993.
4. Kasper, Braunwald, Fauci, Hauser, Longo, James (ed): Harrison's principles of internal medicine. (16th ed.). McGraw-Hill 2005
5. Henry B J (ed.): Clinical Diagnosis and Management by Laboratory Methods. (20th ed.). W.B. Saunders Company 2001

Plasma proteins and laboratory diagnosis of inflammation and infectious diseases

Miłosława Zowczak-Drabarczyk MD

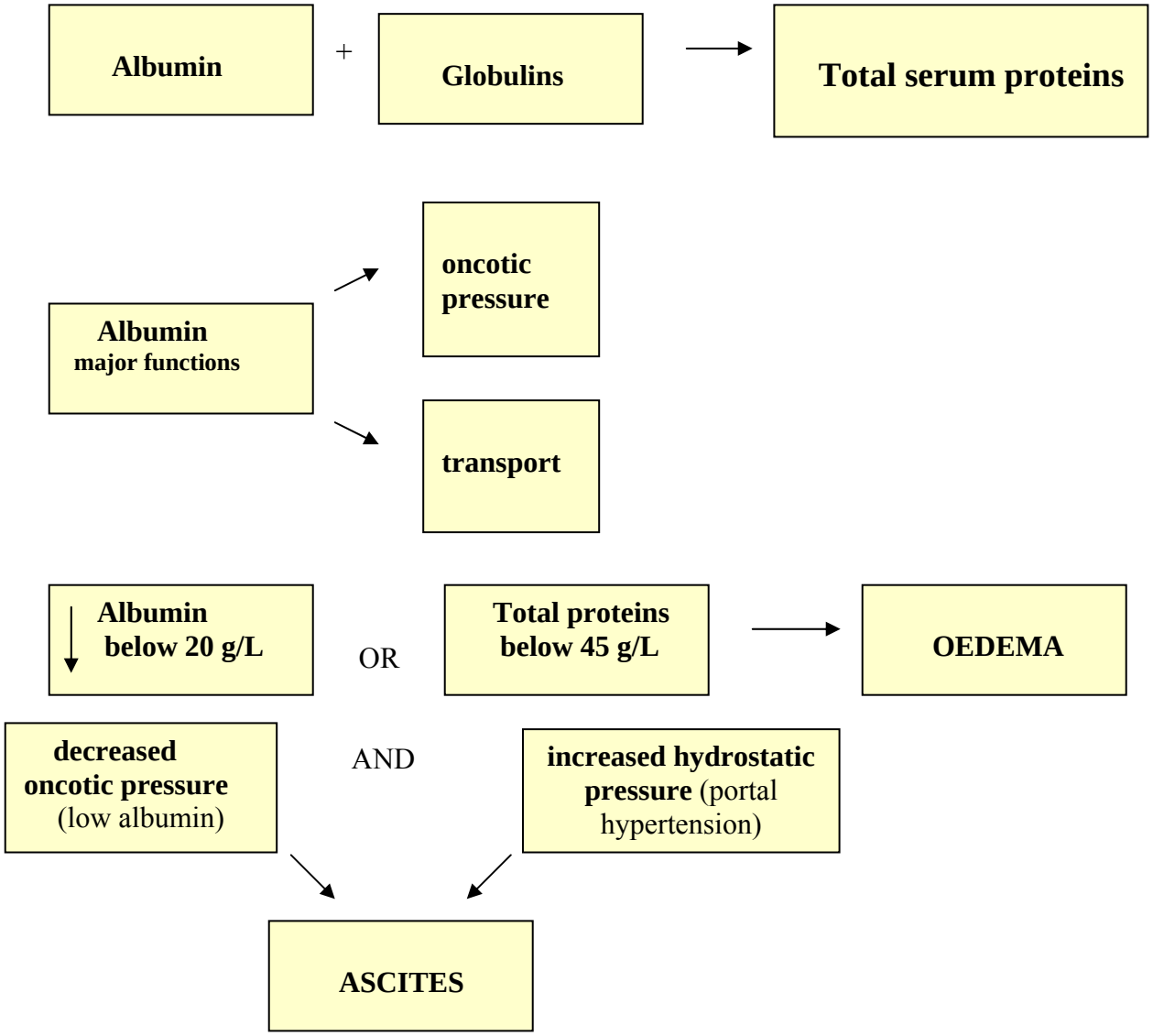
Causes of hypoproteinemia:

With hypoalbuminemia: I. *Impairment of liver protein synthesis*: – malnutrition, malabsorption – hepatocellular disease, primary or metastatic tumor to the liver	III. *Changes in the extracellular space volume→changes in protein distribution:* (pseudohypoproteinemia!) – overhydration – prolonged bed-rest
II. *Increased protein loss*: – through kidney→nephrotic syndrome – through gastrointestinal tract→protein-losing enteropathies (e.g. GI malignancies, Crohn's disease, ulcerative colitis, celiac sprue) – through skin→extensive skin damage (e.g. burns, dermatosis) – with blood→haemorrhage – with exudates (e.g. peritoneal, pleural) – in catabolic states (e.g. sepsis, end-stage neoplastic disease, extensive injury)	IV. *Dilution of the sample with the infusion fluid without protein* (pseudohypoproteinemia!) Without hypoalbuminemia V. *Severe immunoglobulin deficiency* (congenital and acquired)

Causes of hyperproteinemia:

I. *Hypergammaglobulinemia:* 1. Monoclonal gammapathies: – multiple myeloma – Waldenström's macroglobulinemia – heavy-chain diseases – monoclonal gammapathies of undetermined significance – other diseases of lymphatic system	2. Polyclonal gammapathies, e.g.: – chronic inflammation – autoimmune diseases – chronic liver disease
II. *Dehydration* (pseudohyperproteinemia!)	***II.*** *Prolonged use of tourniquet* (pseudohyperproteinemia!)

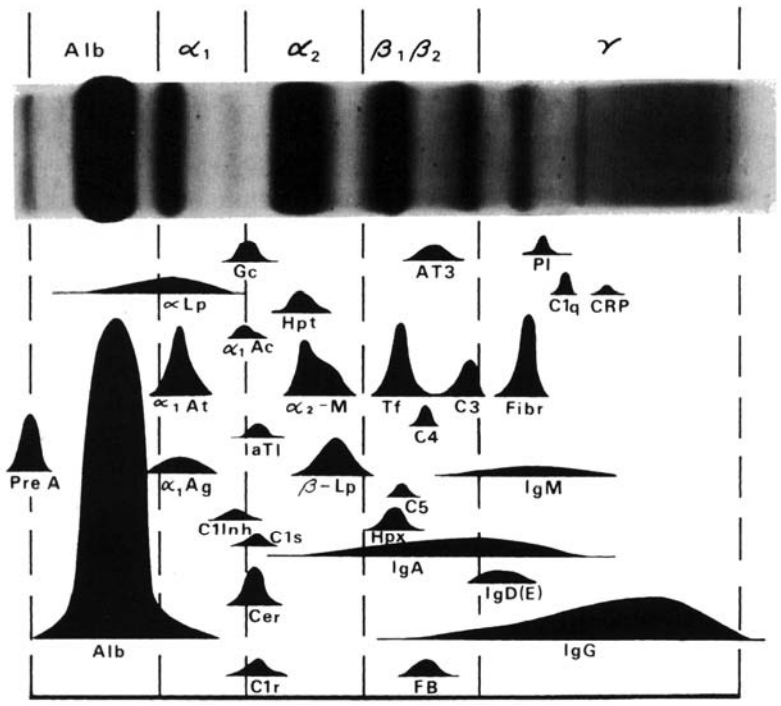
Serum albumin



Normal electrophoretic pattern, reference values

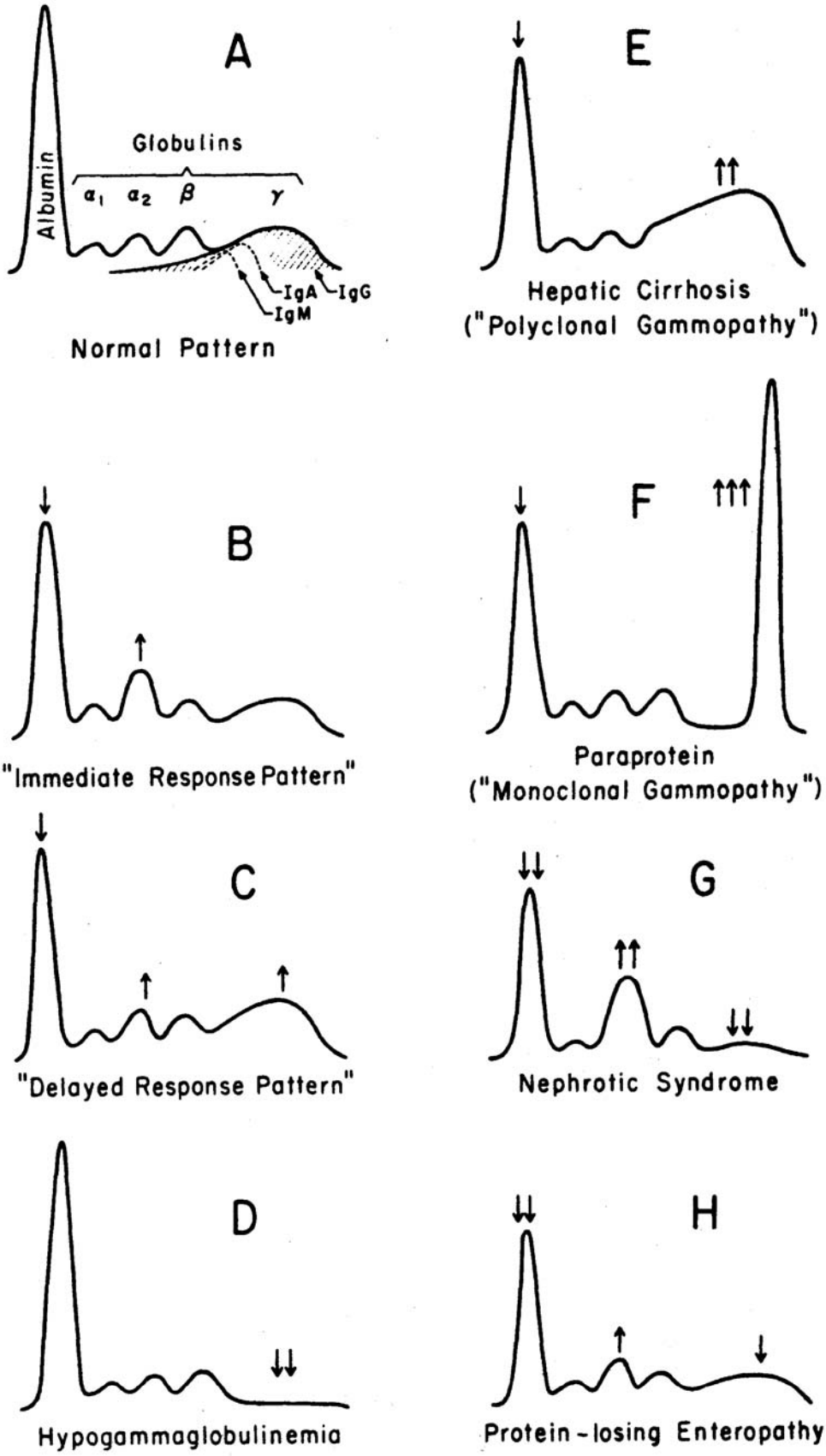
Albumin	35-55 g/L	50 – 60%
Globulin	20-35 g/L	40-50%
α_1	2-4 g/L	2,5-5%
α_2	5-9 g/L	7-13%
β	6-11 g/L	8-14%
γ	7-17 g/L	12-22%

Diagrams: serum protein electrophoresis pattern 1. and 2.



α_1Ac = α_1-Antichymotrypsin
α_1Ag = α_1-Acid glycoprotein
α_1At = α_1-Antitrypsin
α_2-M = α_2-Macroglobulin
α-LP = α-Lipoprotein
Alb = Albumin
AT3 = Antithrombin III
β-Lp = β-Lipoprotein
Complement components:
C1q, C1r, C1s, C3, C4, C5 = As designated
C1Inh = C1 esterase inhibitor
Cer = Ceruloplasmin
CRP = C-reactive protein
Gc = Gc-globulin (vitamin D-binding protein)
FB = Factor B
Fibr = Fibrinogen
Hpt = Haptoglobin
Hpx = Hemopexin
Immunoglobulins:
IgA, IgD, IgE, IgG, IgM = As designated
IaTI = Inter-α-trypsin inhibitor
Pl = Plasminogen
Pre A = Prealbumin
Tf = Transferrin

Serum protein electrophoresis pattern *(after:Henry J.B.: Clinical Diagnosis and Management by Laboratory Methods. 20th ed. W.B. Saunders Company. Philadelphia 2001.,modified)*



Typical serum protein electrophoresis patterns *(after:Henry J.B.: Clinical Diagnosis and Management by Laboratory Methods. 20th ed. W.B. Saunders Company. Philadelphia 2001., modified)*

Protein concentrations in urine, reference values

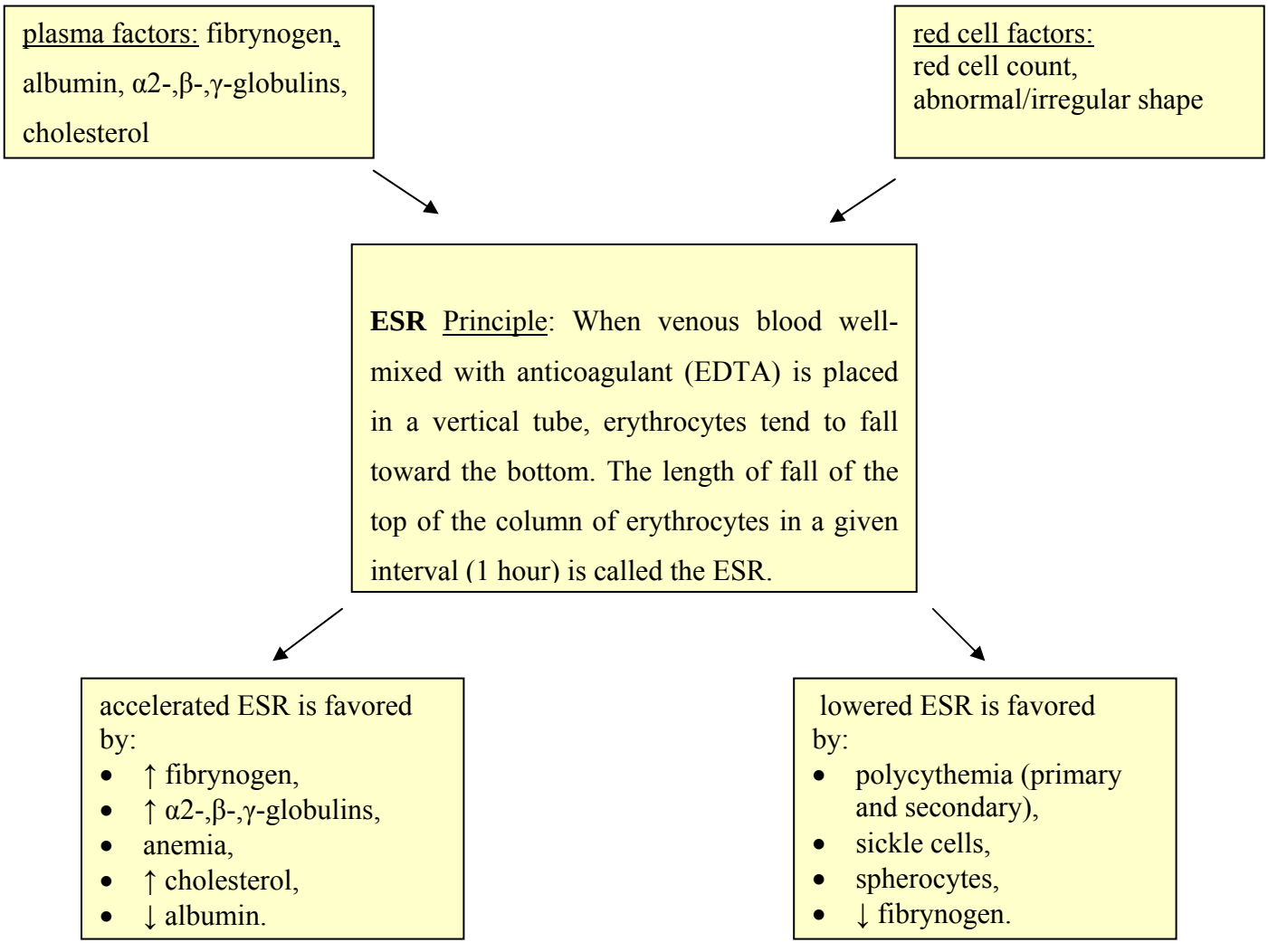
Total protein	< 150 mg/ 24 h collection
Albumin	<30mg/ g of creatinine
Light chains	< 10 mg/ 24 h collection

Microalbuminuria: 30-300 mg of albumin/ g of creatinine in 2 out of 3 consecutive tests

Macroalbuminuria: > 300 mg of albumin/ g of creatinine in 2 out of 3 consecutive tests

Erythrocyte sedimentation rate (ESR), reference values

	Men	Women
Newborns	0-5 mm/1 h	0-5 mm/1 h
Infants	17 mm/1 h	17 mm/1 h
Below age 50 years	15 mm/1 h	20 mm/ 1 h
Above age 50 years	20 mm/1 h	30 mm/1 h
Above age 85 years	30 mm/1 h	42 mm/1 h



Interpretation: ⟶ ***Physiologically***, the ESR ***increases*** moderately during ***menstruation***, in ***pregnancy*** (beginning at the tenth to twelfth weeks, and return to normal about one month postpartum), and with aging (***above 50 years***).

⟶ The ESR tends to be markedly elevated in monoclonal blood protein disorders, in severe polyclonal hyperglobulinemias due to inflammatory disease or cancer and in hyperfibrynogenemia.

⟶ **Moderate elevations of ESR** are common in **active inflammatory diseases** such as rheumatoid arthritis, **infections (especially bacterial**), **collagen disease**, and **malignancy**. ESR has little diagnostic value in these disorders, but it can be useful in monitoring disease activity.

⟶ ***ESR normal does not exclude any pathology***.

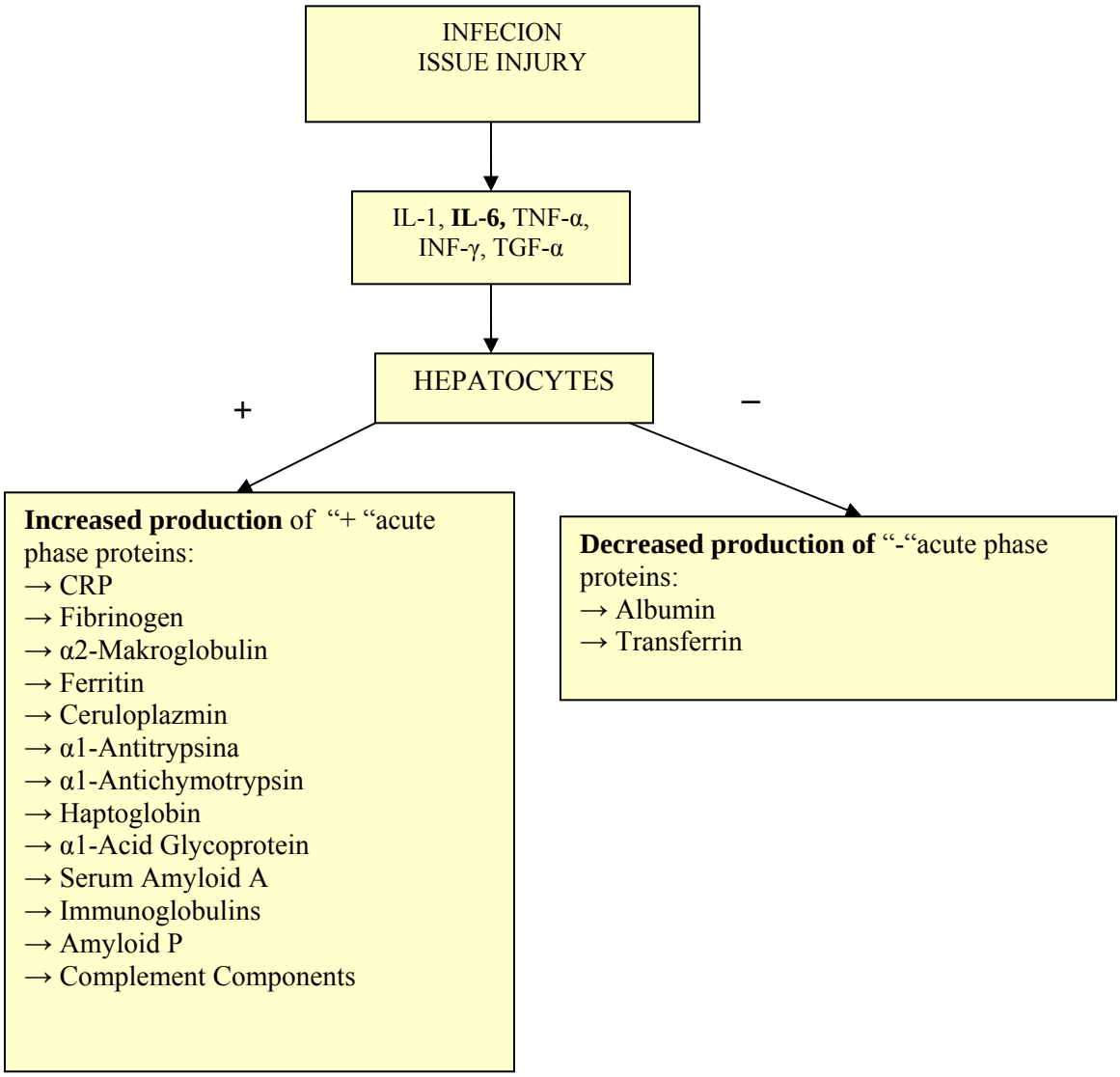
C- Reactive Protein (CRP)

CRP is generally useful acute phase reactant for diagnosing and monitoring inflammatory response. CRP is the fastest rising acute phase protein and one that returns to normal quickly following successful therapies: it begins to rise 4-6 hours after onset of inflammation and its T1/2 is only 5-7 hours.

Classical CRP assay methods: CRP is frequently applied to the detection and preliminary classification of occult infection because bacterial infection can stimulate much higher CRP levels than viral ones. It is also wildly used for assessing disease activity in autoimmune disorders (e.g. in very active phase of rheumatoid arthritis it can rise 20-fold). The normal serum concentration of CRP is up to 10 mg/L (in some laboratories up to 5 mg/L).

Ultrasensitive CRP assay methods: CRP is an independent prognostic factor of acute cardiac incident (ACI) n primary and secondary prevention. Low risk of ACI when CRP < 1mg/L,
increased risk of ACI when CRP 1-3 mg/L, high risk of ACI when CRP >3 mg/L.

Production of acute phase proteins



PROCALCITONIN:

- **better** marker **than CRP for discrimination** of **SIRS from sepsis** and for the **monitoring** of patients with **sepsis**
- **better correlates with outcomes** of **antibiotic therapy than CRP**

Urinalysis and other laboratory procedures in the diagnosis of the urinary tract disorders

Hanna Kara-Perz MD, Dorota Formanowicz MD

URINE EXAMINATION

Quantity of urine excretion:

***Normal urine*: 1000-1500 ml of urine per day**

***Oliguria*: <500 ml of urine per day** (is present when the urine flow rate is less than the minimum required to allow excretion of daily solute load

Anuria: **<100 ml of urine per day** or **the complete absence of urine flow**

- in general, the causes of anuria and oliguria are the same as hose of acute renal failure

Polyuria: is a term, indicating passage of large volume of urine, but implying nothing about the appropriateness (or otherwise) or cause of the high urine flow rate

- causes: excessive water intake (psychogenic poydipsia), osmotic diuresis (diabetes mellitus (glucose), chronic kidney disease (urea), abnormal tubular water handling

Physical evaluation

Urinary pH - mean 6,2 (4,6-8,0)

Alkaline urine suggests:	Acid urine suggests:
• vegetarian diet • alkali ingestion (sodium bicarbonat,potassium citrate) • infection with urea-splitting organisms • metabolic alkalosis • respiratory alkalosis (acute) • renal tubular acidosis (type I) • water diuresis	• high protein diet • acid ingestion (ascorbic acid, ammonium chloride) • potassium depletion • metabolic acidosis • respiratory alkalosis (acute) • hyperaldosteronism • water deprivation • intoxication of methyl alcohol

Colour

Normal urine - pale, straw-yellow colour (due to the presence of the pigment urochrome), it may also appear deep amber or almost colourless

Discoloration (as a result of pathology or secondary to the presence of drug or food)

- **orange urine:** bile pigments, nitrofurantoin, phenothiasines, rhubarb, carrot, senna
- **yellow urine:** bile pigments, rhubarb, carrot, nitrofurantoin, phenacetin
- **green:** biliwerdin, methylene blue, nitrofurans, vitamin B complex
- **blue-green, blue urine:** nitrofurans, methylen blue
- **red urine:** RBC, myoglobin, hemoglobin, porphyrins, bromsulfophtalein, phenytoin, senna, beetroots
- **brown or black urine:** biliary pigments, hematin, myoglobin, iron salts, nitrofurans, sulpha drug

Odour

- **ammonia odour**: break-down of urea in the urine
- **purgent aroma:** UTI, high ammonia conc., failure to deliver the specimen to the laboratory in the fresh state
- **other very characteristic odours**: maple sirup urine disease, phenylketonuria, isovaleric acidemia

Turbidity (phosphates, leukocyturia, bacteriuria, chyluria)

Specific gravity

- The **normal** spectrum of urinary specific gravity results for random specimens ranges from **1.003 to 1.040**
- The specific gravity of a **first-morning specimen** should be greater than **1.015**
- **Very high values**- presence of glucose or protein
- **Dilute urine –** high fluid intake, tubular disorders, diuretics administration, early glomerular disease
- **Very dilute urine (between 1.001 and 1.005)-** extremely high fluid intake, diuretics administration, diabetes insipidus

Chemical evaluation

Protein

Normal urine*: ≤150 mg per day**, with exception of ***orthostatic proteinuria

The protein excretion rate is generally increased in the up-right posture, and, on occasion, this may lead to abnormally high protein measurements in timed collections or spot measurements in normal ambulant subjects. This is termed *orthostatic proteinuria* and the diagnostic difficulty may be resolved by demonstrating that an-early-morning urine specimen is normal while a specimen taken later in the day with the subject ambulant contains excess protein

***Proteinuria*: >150 mg per day**

DEGREE OF PROTEINURIA	DIAGNOSTIC IMPLICATIONS
MILD (up to 500 mg/day)	• fever • benign hypertensive nephrosclerosis • renal tumour • obstructive nephropathy • chronic pyelonephritis • early diabetic nephropathy • orthostatic proteinuria
MODERATE (up to 3 g/day)	• urinary tract infection (UTI) • chronic pyelonephritis • acute tubular necrosis • acute/chronic glomerulonephritis • obstructive nephropathy • accelerated phase hypertension • orthostatic proteinuria
HEAVY (more than 3 g/day)	• pre-eclampsia • myeloma • acute/chronic glomerulonephritis • diabetic nephropathy • all causes of nephrotic syndrome

Categories of proteinuria:

1. **Prerenal proteinuria**
   - the first type - abnormal low molecular weight protein easily passes through the glomerulus into the urine
   - the second type - change in hydrostatic pressure in the kidney glomerulus
2. **Glomerular proteinuria**
   - in the **earliest stages** of glomerular damage proteinuria is *selective* and the urinary proteins are the lowest molecular weight proteins found in the bloodstream
   - in the **advanced stages**, if glomerular damage progresses, all of the proteins found in the blood may appear in the urine (*non-selective proteinuria*)
3. **Tubular proteinuria**
   - generally mild, low molecular weight
   - usually secondary to: tubular damage, heavy metal intoxication, vitamin D intoxication, galactosemia, pyelonephritis, acute tubular necrosis, polycystic kidney disease
4. **Mixed proteinuria**
   - β_2 microglobulin is mainly excreted (glomerular and tubular damage)
5. **Lower urinary tract proteinuria**
   - exudation of protein through the mucosal layer of the lower urinary tract
   - secondary to UTI
6. **Asymptomatic proteinuria** - orthostatic

Albumin

- ***normal urine*:** urinary albumin excretion less than 30 mg/24h, urine albumin concentration less than 20 mg/l
- ***microalbuminuria*** – urinary albumin excretion rate from or **30-300 mg/24h** (urine albumin concentration ranges from **20 to 200 mg/l**) – predicts the later development of clinical diabetic nephropathy
- ***macroalbuminuria*** - urinary albumin excretion rate **>300 mg/24h** (urine albumin concentration > **200 mg/l**)

Glucose

- glucose is filtered through the glomerulus
- body reclaims this filtered glucose in order to prevent the loss of carbohydrate energy (active transport reabsorptive mechanism)
- when the plasma glucose conc. exceeds 10 mmol/l the reabsorptive capacity of the tubules is exceeded

Ketones

Increased fat metabolism leading to ketoacidosis occurs in:

- **starvation**
- **insulin-deprivation**

Hemoglobinuria

Causes:

- **intravascular hemolysis:** when the capacity of haptoglobin or hemopexin to bind and remove haemoglobin is exceeded, the free haemoglobin passes through the glomerulus into the urine
- **glomerular disease**: hemoglobinuria may be associated with the presence of red cells and red-cell casts in the urine
- **bleeding from the lower urinary tract**: it may be accompanied by red cells, but never red-cell casts

Myoglobinuria

Causes:

- crush injuries
- heavy exercise
- grand mal seizures
- coma
- myopathies

Bilirubinuria

- appearance of conjugated bilirubin in the urine is strong evidence for obstruction lesion in the liver or biliary system

prehepatic jaundice (↑ unconjugated bilirubin)	absence
hepatic jaundice (↑ unconjugated and conjugated bilirubin)	presence
posthepatic jaundice (↑conjugated bilirubin)	presence

Urobilinuria

- increased urobilinogen can be found in the urine of those suffering from hepatocellular liver disease or hemolytic process

prehepatic jaundice	↑
hepatic jaundice	↑/↓
posthepatic jaundice	↓

Leukocyte esterase

- presence of this esterase → presence of white cells in the urine

Nitrite

For the test to be positive:

- patients must have nitrate in the urine (production associated with the consumption of vegetables)
- only certain bacteria have the ability to produce nitrate-nitrite conversion

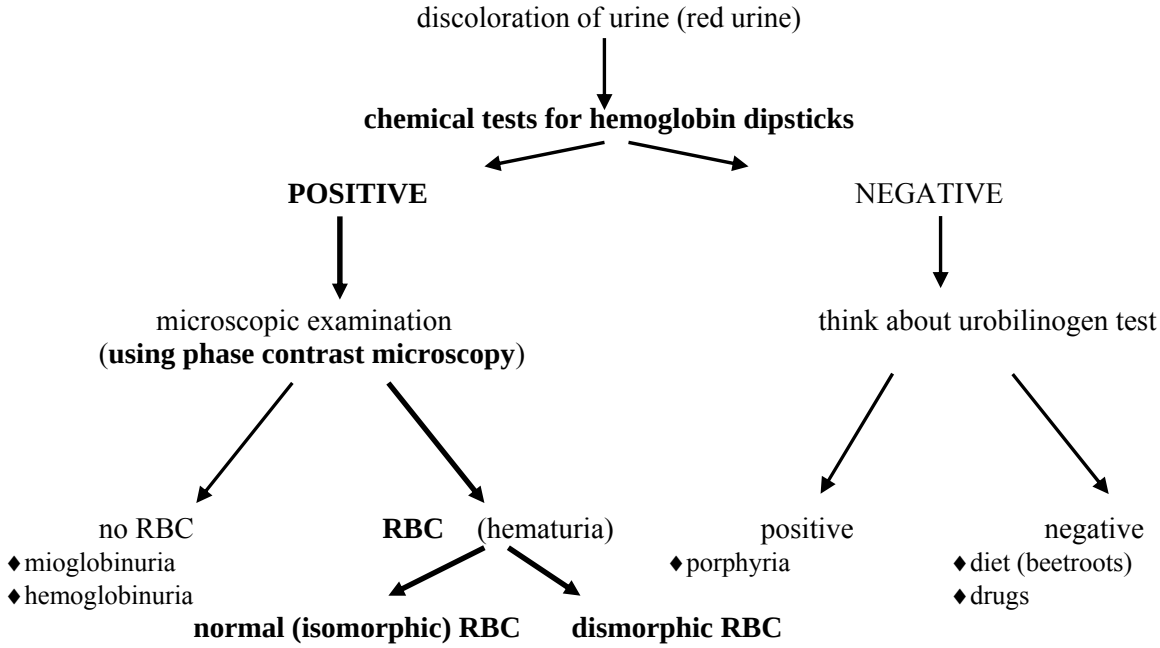
- **presence of nitrite** → presence of bacteria in the urine
- **negative test** → does not exclude the presence of UTI

Microscopic examination: *Formed elements of the urine*

1. red blood cells
2. white blood cells
3. epithelial cells
4. microorganisms
5. crystals
6. casts

1. Hematuria - more than 5 RBC/1 μl of urine

- ***microhematuria*** (***erythocyturia***)- **>5 RBC/1μl of urine** or **>3000 RBC/1ml of urine**, these amounts of RBC are insufficient to cause visible discoloration of urine
- ***macrohematuria*** - more RBC than in microhematuria, with visible discoloration of urine



A positive test for hemoglobin should always be followed by microscopic examination for RBC (using phase contrast microscopy)

This will distinguish hematuria from hemoglobinuria and also may indicates whether RBC are derived from:

- the renal parenchyma - **dismorphic RBC** (*are usually indicators of glomerular bleeding*)
- the collecting systems, ureters, bladder **– normal (isomorphic) RBC**

The causes of hematuria include:

- **lower urinary tract lesions: tumours**, trauma**, calculi**, infection, congenital malformations, prostatic disease, stricture

- **upper urinary tract lesions**: tumours, trauma, calculi, infection, congenital malformations, renal arterial or venous disease, certain interstitial diseases, **glomerulonephritis**
- bleeding disorders associated with haematological disease or due to anticoagulant drugs disease adjacent to and impinging on the urinary tract

2. Leukocyturia more than 10 WBC/1 μl of urine

- ♦ usually present in UTI
- ♦ ***pyuria*** – cloudiness of urine caused by the large amounts of WBC

3. Epithelial cells

Three major types of epithelial cells in the urine

- squamosus
- transitional
- renal tubular cells

presence of moderate numbers of epithelial cells → no medical significance

presence of large numbers of epithelial cells → poor specimen collection

4. Microorganisms

- although **bladder urine should be sterile**, **voided urine is not**, and interpretation of bacteriological studies of urine must take account of this
- contamination is minimized (though not eliminated) by use of the midstream urine (MSU), in which the initial part of the voided stream is discarded and the mid- portion of the stream collected in a sterile container
- the likelihood of significant infection is high if:
    - a pure growth of single organism is obtained (multiple organisms often indicate contamination)
    - the number of bacteria **exceeds 10^5/ml**
    - leucocytes are present in the spun deposit of fresh urine

5. Crystals

They form as a result of precipitation of inorganic salt contained in the urine

- cystine crystals – hereditary cystinosis
- leucine and tyrosine crystals
    - serious hepatic damage
    - hereditary metabolic disorder
- drug crystals (sulfa crystals, ampicyllin crystals)
- uric acid crystals – acidic urine
- phosphates and calcium carbonate crystals – alkaline urine

6. Casts *(collection of protein and cellular debris)*

- urinary casts consists of Tamm-Horsfall protein derived from the tubular epithelium
- formed in the distal nephron
- Tamm-Horsfall protein is alkali-soluble, so **there is no casts in alkaline urine**

Types of casts

- **hyaline** casts
  theirs origin is tubular secretion of Tamm-Horsfall protein
  presence may be nonspecific or may be due to glomerulonephritis, pyelonephritis, chronic renal disease, congestive heart failure, stress, exercise
- **red blood cells** casts
  any conditions that damage the glomerulus, tubules or renal capillaries
- **white blood cells** casts
  are rarely true cast
  UTI
- **epithelial** casts
  acute inflammatory process (glomerulonephritis, pyelonephritis)
- **granular** casts
  chronic disorder, rarely seen in acute inflammation
  may represent evolution of epithelial casts in which the cells themselves have degenerated
- **waxy** casts
  severe chronic renal disease
  advanced stage of hyaline casts
- **fatty** casts
  severe renal disease, nephrotic syndrome
  breakdown product of epithelial casts that contain fat bodies
- **broad** casts
  ”renal failure casts”
  all types of casts may be present in broad form
- **pseudo** casts
  epithelial cells, WBC, RBC, bacteria may coalescence together, giving the appearance of a cast

Blood examination

UREA - 15 – 40 mg/dl

- major nitrogen-containing metabolite from the degradation of protein
- the **concentration** of urea in blood-stream depends on several factors:
  - **urea production** (**protein intake**, protein and blood in gastrointestinal tract, catabolic states, liver function)
  - **volume of body water** (in which urea is distributed)
  - **rate of urea elimination**

Ethiology of elevated urea level can be categorized as:

- **prerenal** (increased production of urea or decreased renal perfusion)
- **renal** (loss of functioning nephrons)
- **postrenal** (obstruction of the urinary tract)

Blood urea nitrogen (BUN) = uric acid [mg/dl] × 0.46

BUN/creatinine serum concentration ratio	**15:1 [mg: mg]**	reference range
	>20:1	in acute renal failure (prerenal) and in partial obstruction of urinary tract
	<5-10:1	in liver diseases, malnutrition, rhabdomyolisis

If GFR is below 25% of normal values → the serum concentration of urea exceeds its upper bound of normal values

CREATININE - 0,7 – 1,2 mg/dl

Creatine:

- synthesis in the liver
- muscle- total body stores of creatine
- degraded to creatinine

Creatinine

- excretion from the body by glomerulofiltration and secretion (slight) through the tubule

  The **concentration** of creatinine in blood-stream depends on several factors:
  - **creatinine production** (**muscle diseases**, high-meat diet, anabolic steroid use, severe exercise)
  - **volume of body water** (in which creatinine is distributed)
  - **rate of creatinine elimination**

Ethiology of elevated creatinine level can be categorized as:

- **prerenal** (increased production of creatinine or decreased renal perfusion)
- **renal** (loss of functioning nephrons)
- **postrenal** (obstruction of the urinary tract)

If GFR is below 50% of normal values → the serum concentration of creatinine exceeds its upper bound of normal values

URIC ACID - 4,0-8,5 mg/dl (adult male) - 2,7-7,3 mg/dl (adult female)

- major end product of purine metabolism
- hyperuricemia:

  increased production of uric acid (increased de novo synthesis- gout, rapid proliferation of cells, increased catabolism of purines)

  decreased renal excretion of uric acid (renal failure, diuretics, aspirin <2 g/day, metabolic acidosis, toxemia, pregnancy)

Renal function test

GFR

- the most useful index of overall renal function
- amount of plasma ultrafiltred across the glomeruli per unit time (expressed in milliliters per minute)
- calculation of GFR requires a test substance that is freely filtrated at the glomerulus, but neither reabsorbed not secreted by the tubules
- measured indirectly by estimating the clearance from urine of a plasma-borne substance (creatinine)

$$C=U\times V/P$$

C- clearance of creatinine
U- urine concentration of the creatinine (mg/dl)
V- urine flow rate (ml/min)
P- plasma concentration of the creatinine (mg/dl)

- the evaluated clearance of creatinine is usually 10% higher than actual GFR

Normal values:

- men 100-150 ml/min
- women 85-125 ml/min
- first week of life 30 ml/min/1,73 m^2
- up to age 9 months mature levels

GFR declines slowly after age 40 (1ml/minute per year)

↑GFR: during pregnancy, high protein diet, hyperglycemia

↓GFR: limit of fluids intake, excessive loss of fluids (skin, lungs, kidneys, gastrointestinal tract), after using non-steroids anti-inflammatory drugs

If calculated clearance of creatinine amount to ≥10 ml/min → this method for GFR estimation should be avoided, because of measurement error, which may be equal to 100%

Relationship between creatinine clearance and plasma creatinine concentration:
Renal blood flow (RBF) and renal plasma flow (RPF)

not commonly measured in clinical medicine

RBF is high: about **25% of the resting cardiac** output, or 1300 ml/min, this corresponds to a RPF of 700 ml/min, of which **25% is ultrafiltred at the glomeruli**, giving GFR

Fractional excretion of sodium (FE_{Na})

$$FE_{Na}=U_{Na}\times P_{Cr} / U_{Cr}\times P_{Na}$$

U_{Na}- urine sodium concentration
P_{Cr}- plasma creatinine concentration
U_{Cr}- urine creatinine concentration
P_{Na}- plasma sodium concentration

(as a percentage of filtered sodium can be determined from single blood and urine samples)

FE_{Na} >1%

- acute tubular necrosis

FE_{Na} <1%

- prerenal azotemia

DISEASES

SYMPTOMS AND SIGNS OF RENAL AND URINARY TRACT DISEASE

renal pain	**hematuria**	
		macroscopic
		microscopic
auria/oliguria	**proteinuria**	
		asymptomatic
		symptomatic (nephritic syndrome)
polyuria	**hypertension**	
frequency	**oedema**	
		periheral
		pulmonary
dysuria	**uraemia**	
incontinence		

1. Urinary tract infections (UTI)

a working definition of UTI is the presence, in an appropriately collected mid-stream specimen of urine, of **more than 10^5 colony** forming units per ml of urine → this is merely an arbitrary limit above which significant infection is likely

SIGNIFICANT BACTERIURIA means ≥$10^{4(5)}$/ 1ml of midstream, clean-catch urine sample

- ***Enterobacteriaceae***
  - bacterial counts <10^4/1ml – usually contamination
  - bacterial counts ≥10^5/1ml in asymptomatic female-two specimens should be obtained to confirm the diagnosis
- ***Gram-positive, fungi, bacteria with fastidious growth requirements***
  - bacterial counts ≥10^4/1ml may indicate UTI

Microscopic examination (nonspecific changes):

- **pyuria** (many patients with symptomatic UTI have pyuria)
  - ***sterile pyuria*** is defined as white cells in the urine in the absence of significant bacterial growth

Causes of sterile pyuria

- recently treated urinary infection
- tuberculosis
- acute interstitial nephritis
- chronic interstitial nephritis (including analgesic nephropathy)
- chronic pyelonephriis

- **white cells cast** (especially in pyelonephritis)
- **mild proteinuria**
- **hematuria** (hemorrhagic cystitis or other disorders such as calculi, glomerulonephritis, renal tuberculosis)

Predisposing factors to development of UTI:

1. **Female sex**
2. Failure of complete bladder empting (e.g. prostatic hypertrophy, neurological disease)
3. Anatomical disorders of bladder (e.g. blader diverticulum)
4. Vesicoureteric reflux (reflux of urine into ureters or kidney during micturition)
5. Pregnancy (the ureters and renal pelves dilate during normal pregnancy)
6. Diabetes mellitus (only in patients with long standing disease)
7. Tumorurs (**! UTI may be the first sign of an underlying bladder tumour**)
8. Stones (the presence anywhere in the urinary tract makes infection more likely)

UTI include

- **urethral syndrome** (the combination of dysuria, frequency, urgency and strangury)
- **the clinical entities of cystitis** (symptoms are those of the urethral symptoms and are accompanied by pyuria and significant bacteriuria; the urine is usually cloudy, and may be foul-smelling) → the infection may ascend leading to acute pyelonephritis
- **acute pyelonephritis** (usually results from ascending infection, diabetics, and subjects with obstruction of the urinary tract are at particular risk)
- **asymptomatic bacteriuria**

  in adults, the incidental finding of significant bacteriuria is generally <u>of little consequence</u> (antibiotic therapy is not value) - with exception:

  - pregnant women **showing a propensity for the asymptomatic bacteriuria to progress to cystitis and acute pyelonephritis**
  - **children with vesicoureteric reflux**

UTI may occur as a single event or may be reccurent as relapses or reinfections
Chronic UTI means persistent urinary tract infection

Localization of infection

- invasive techniques
- non-invasive technique (bacteria in urine of renal origin are coated with antibody)

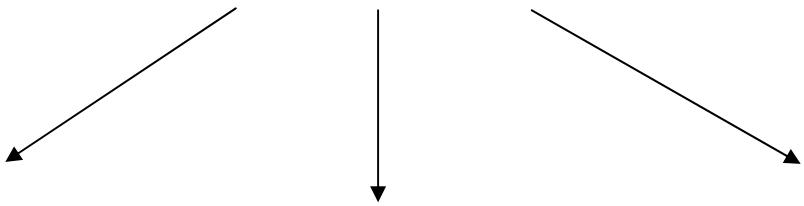
2. Urolithiasis (urinary stone)

The most important **constituents of urinary stones** are:

The most important **constituents of urinary stones** are:

	frequency (%)	radio-opaque
- calcium oxalate + hydroxyapatite	45	++
- calcium oxalate	35	++
- magnesium ammonium phosphate + calcium phosphate (**struvite**)	10	++
- uric acid	5	**0**
- calcium phosphate	1-3	++
- cystine	1-2	+

Laboratory examination:



Diagnosis — **risk factors** — complications

- **chemical examination** (stone's composition - usually connected with individual features of metabolism)
- **daily urinary excretion of substances which may be constituents of urinary stones:**

	the upper limit of normal	
calcium	5 mmol/d	(200 mg/d)
oxalate	0,45 mmol/d	(40 mg/d)
uric acid	4,75 mmol/l	(800 mg/d)
phosphate	38,0 mmol/l	(1,2 g/d)
cystine		(400 mg/d)

other indexes concerning calcium and oxalate excretion:
calcium/creatinine ratio < 0,69 mmol/mmol (0,21 mg/mg)
magnesium/calcium ratio> 0,8 mg/mg

- **blood concentration of substances which may be constituents of urinary stones:**

calcium	2,25-2,65 mmol/l	
uric acid	180-420 μmol/l	(3-7 mg/dl)
phosphate	0,9-1,6 mmol/l	(3-5 mg/dl)
oxalate	33-77 μmol/l	(0,3-0,7 mg/dl)

- **urinalysis** (nonspecific abnormalities)
  - **erythrocyturia**
  - **leukocyturia-**presence of stones in the urinary tract may -maintain UTI, and UTI is one of the contributing factors for stone's precipitation
  - **cristals**
  - **urine pH-** calcium phosphate and magnesium-ammonium phosphate stones- cristallize in alkaline urine, uric acid and cystine- acid urine
  - **specific density-** indirect information about patient's fluid intake

3. Nephrotic syndrome

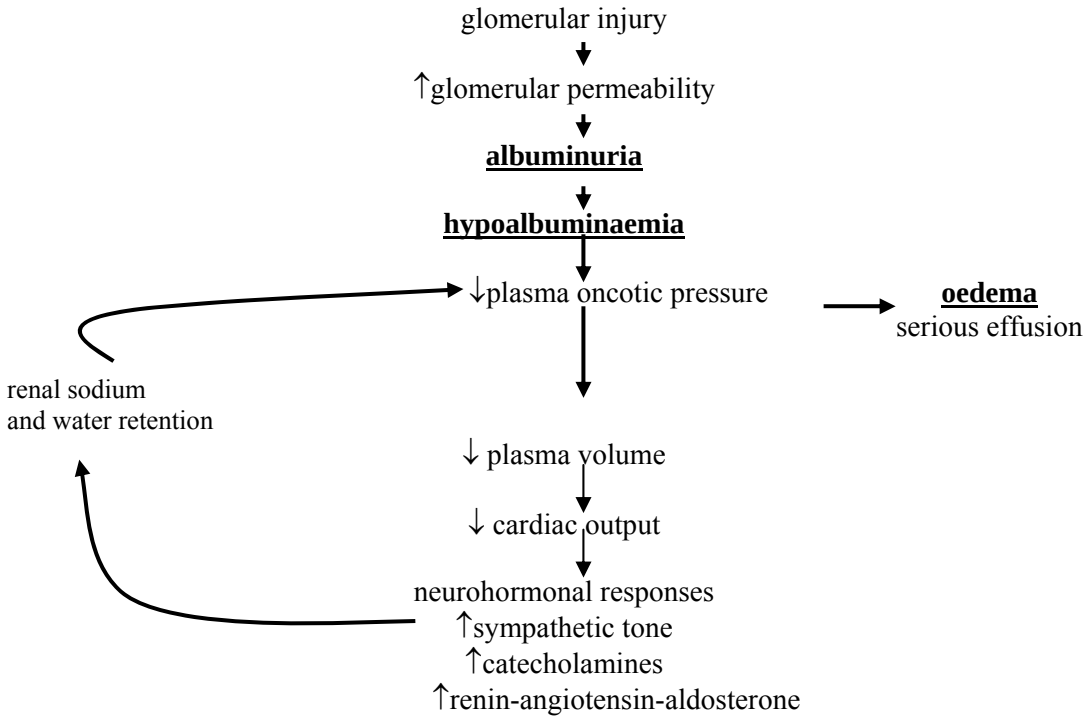
clinical syndrome of diverse etiology characterized by the triad:

proteinuria (>3,5 g/1,73 m^2/day) **hypoalbuminemia** **oedema**

Proteinuria
- due to **increase in glomerular permeability**
- proteinuria is influenced by: GFR, plasma conc. of albumin, dietary protein intake

Hypoalbuminemia
- due to:
  proteinuria
  inadequate hepatic synthesis of albumin
  increased renal catabolism of proteins

Oedema



Hyperlipidemia
characteristic changes observed in serum lipids include:
- increase in low-density lipoproteins (LDL)
- increase in very low-density lipoproteins (VLDL)
- decrease in high-density lipoproteins (HDL)

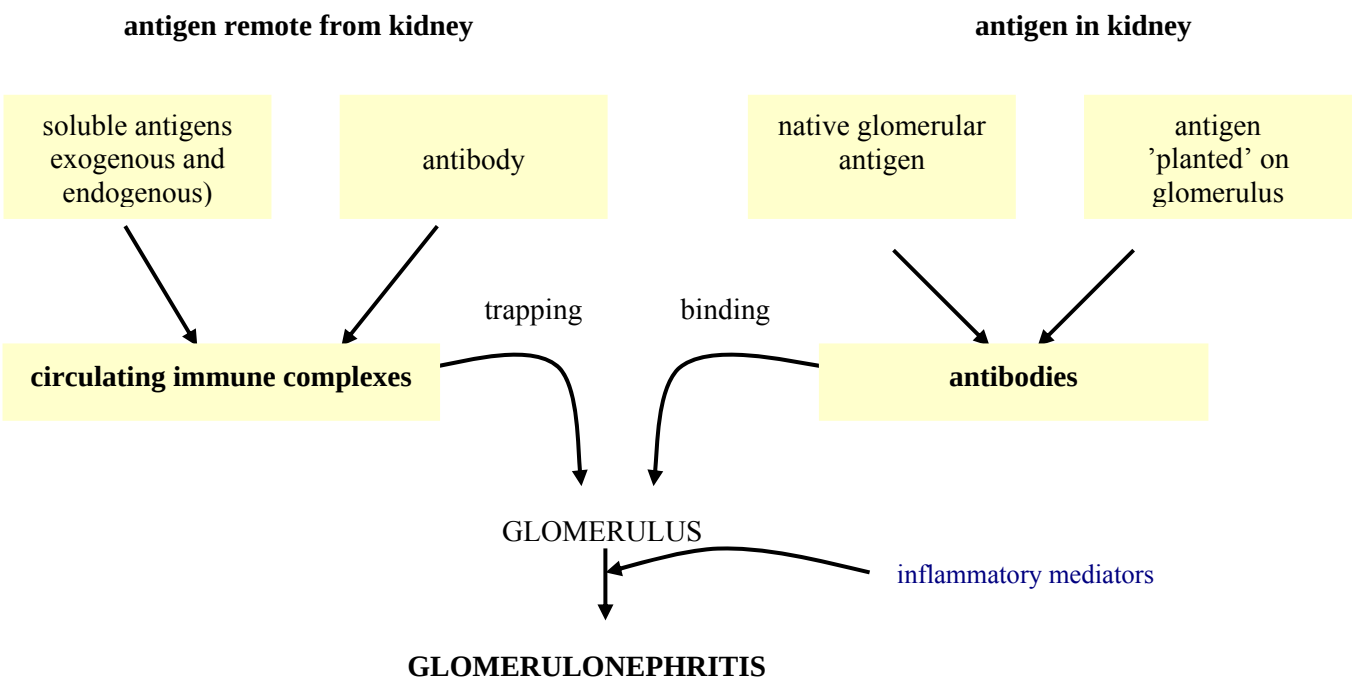
decreased plasma oncotic pressure and/or the hypoalbuminemia stimulate hepatic lipoprotein synthesis

Lipiduria
lipid-containing epithelial cells (oval fat bodies)

Hypercoagulability
is attributed to several factors:
- hypoalbuminemia may induce increased hepatic synthesis of fibrinogen and procoagulant factors and increased platelet aggregation
- high alpha-2-macroglobulin concentration and low plasminogen concentration, which result in a decrease in the plasma fibrinolytic activity
- the presence of hypovolemia and hemoconcentration
- antithrombin III loss

4. Glomerulonephritis

mechanisms of immunological renal injury



specific glomerular disease

- acute nephritic syndrome
- rapidly progressive glomeulonephritis (RPGN)
- chronic glomeulonephritis→chronic kidney disease (CKD)
- nephrotic syndrome
- asymptomatic haematuria and-or proteinuria
- recurrent macroscopic haematuria
- acute glomerulonephritis

•**acute nephritic syndrome**
- characterised by:

abrupt appearance of blood (haematuria microscopic or macroscopic (dysmorphic RBC)) and protein (up to 3 g/day) hin urine, spun deposit of urine contains RBC and casts cellular, granular or both)

- **decline in GFR**
- **hypertension**
- **sodium and water retention**

- causes:

Primary postinfectious	**Secondary with underlying multisystem disease**
	SLE
Baterial	Goodpasteure's syndrome
Streptococci	Henoch-Schonlein purpura
Meningococci	Polyarteritis
endocarditis	Wegener's granulomatosis
Viral	**Other**
CMV, HBV, EBV	idiopathic rapidly progressive glomerulonephritis

•**rapidly progressive glomeulonephritis (RPGN)**

- renal function deteriorates **progressively** over days, weeks or months (usually within the period of 3 months), with urine containing many casts, RBC and proteins, decline in GFR
- causes: multisystem diseases (see above) or infective endocarditis

•**recurrent macroscopic hematuria**

- most frequently affects boys and young males
- is dominated by recurrent episodes of macroscopic hematuria
- sometimes associated with loin pain
- with tendency to exacerbations following intercurrent viral upper respiratory infections or strenuous exercise
- microscopic hematuria persists between attacks and proteinuria is less than 1.5 g/24 hours.
- it is caused by mesangial depostition of IgA in the glomeruli (it is termed IgA nephropathy)

•**acute glomeulonephritis** is suggested by:

- a sudden appearance of hematuria
- edema
- hypertension

sometimes also:
- variable degree of proteinuria
- renal failure
- leukocyturia (not connected with UTI)

Diagnosis:
evaluation of freshly voided **urine** sample:
- erythrocytes (significant numbers, dysmorphic RBC)
- erythrocyte casts
- proteinuria (mild or nephrotic)

blood test:

- BUN, serum creatinine
- serum electrolytes
- complete blood count (RBC- hypochromic-microcytic or normochromic-normocytic anemia, WBC- ↑/↓, PTL↑/↓)
- immunological examination: serum complement components, serologic test for antinuclear antibody, ASL
- bacteriological examination (according to suspected place of infection)

Kidney failure and clinical basics of hemodialysis

Dorota Formanowicz MD

ACUTE RENAL FAILURE (ARF) – prerenal, renal, postrenal

the rapid reduction or cessation of renal function over a period of hours or days
causes:

PRERENAL
- any cause of shock (a low cardiac output)
  - hypovolaemia
  - sepsis
  - cardiogenic
- renal arterial or venous disease: renal artery stenosis, renal vein thrombosis
- inappropriate renal vasoconstriction

RENAL
- acute tubular necrosis, acute glomerulonephritis, acute tubulointerstitial disease, exo/endogenous nephrotoxins

POSTRENAL
- any causes of obstruction (stone, pelvic malignancy, retroperitoneal disease)

1. PRERENAL - decrease in blood flow →reabsorption of salt and water

- **urine sodium concentration <10-25 mEq/l**
- **FE_{Na} <1%**
- **the urine osmolality > 500 mOsm/l**
- **no parenchymal damage**
- **urinalysis is normal** (sometimes only granular or hyaline casts, minimal proteinuria, high specific gravity)
- urine creatinine concentration rise → **high urine/plasma creatinine ratio**
- urine urea concentration rise → **high urine/plasma urea ratio**
- during low flow conditions, more urea is reabsorbed → **high plasma urea/creatinine ratio**

feature		favors prerenal cause	favors renal cause
♦identifiable prerenal factor (shock, hypovolaemia)		yes	no
♦urine	•protein	+	++/+++
	•RBC	0	+/++
	•WBC	0	+/++
	•casts	0/+	+/++
	osmolality (mosmol/kg/ H2O)	>500	<400
	sodium (mmol/l)	<20	>35
♦urine/blood urea nitrogen (BUN) ratio		>8	<3
♦urine/plasma creatinine ratio		>40	<20
♦FE_{NA}		<1%	>1%

2. RENAL

Acute tubular necrosis (ATN)

- Urinalysis- granular casts, renal tubular epithelial cells, small amounts of protein
- **BUN** - rate of rise of BUN is about 10-20 mg/dl/day (in states associated with increased synthesis or decreased elimination of BUN it may exceed 100 mg/dl/day)
- **Serum creatinine** - rate of rise of serum creatinine is about 0.5-1.0 mg/dl/day
- **Metabolic acidosis** - retention of hydrogen ions (in the form of sulphuric and phosphoric acids) results in a decrease in the serum bicarbonate conc.
- **Hyperkaliemia** - serious and life-threatening complication of ARF, may be aggravated by exogenous potassium load (potassium-containing antibiotics, salts substitutes), drugs that impair renal or extrarenal potassium handling, metabolic acidosis, tissue breakdown **Hyponatremia** - result of excessive water ingestion
- **Hypocalcemia** - reasons: hypoalbuminemia, hyperphosphatemia, resistance to parathyroid hormone, reduction in active component of vit. D
- **Hypermagnesemia** - rarely clinically significant
- **Hyperuricemia** - may accompany ATN
- **Hematologic alterations:**
    - **anemia** (decreased erythropoesis, hemolysis, shortened RBC survival, blood loss)
    - **bleeding diathesis** (in ATN alterations in platelet aggregation and adhesivenes)
    - **alteration in the immune system** (lymphopenia, impaired cellular immunity)

3. POSTRENAL ARF- similar laboratory like during prerenal failure are found

Diagnostic features distinguishing between
ACUTE RENAL FAILURE AND CHRONIC KIDNEY DISEASE

Favors ACUTE	Favors CHRONIC
• known recent onset • known precipitating factors • near normal hematology • normal size kidneys (ultrasound, X-rays)	• history of nocturia • pigmentation • normochromic anemia • small kidneys • bone disease (radiographic and biochemical)

CHRONIC KIDNEY DISEASE (CKD), CHRONIC RENAL FAILURE (CRF)

National Kidney Foundation (NKF) definition of CKD:

GFR < 60 ml/min/1.73 m^2 for ≥ 3 months, with or without kidney damage
or
kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by either

- pathologic abnormalities
- markers of kidney damage, including abnormalities in the composition of the blood, or urine abnormalities in imaging tests

Causes of CKD:

- vascular (**hypertensive nephrosclerosis**, renal artery stenosis, systemic sclerosis, vasculitis)
- glomerulopathy
- tubuloinsterstitial nephropathy
- infection and/or reflux (chronic pyelonephritis, renal tuberclosis)
- cystic disease
- obstructive nephropathy
- **diabetic nephropathy**
- amyloid
- renal dysplasia, hypoplasia, agenesis

assessment of the patient who appears to have CKD

histology
renal biopsy – only if kidneys are not small and there is doubt over chronicity

clinical
- symptoms or signs of uremia
- length of history
- family history of
- renal disease
- DM, SLE
- symptoms or signs of obstruction
- volume depletion
- blood pressure /signs of accelerated hypertension

laboratory
- urine analysis for blood/protein, microscopy of fresh spun deposit, culture
- assessment of GFR
- 24-hour protein excretion
- full blood count, ESR
- immunological studies (optional, depending on case)
- HbsAg, Hepatitis C antibodies

imaging
- abdominal X-ray
- ultrasound of kidneys
- radionuclide studies
- hand X-rays (secondary hyperparathyroidism)

Staging and management of CKD (according to Kidney Disease Improving Global Outcomes (KDIGO, 2005)

Stage	Description	GFR ml/min/ 1.73 m^2	Classification of CKD by severity Clinical presentation	Related terms	Action
1	kidney damage with normal or ↑ GFR	**≥ 90**	markers of damage (nephritic syndrome, nephritic syndrome, tubular syndromes, urinary tract symptoms, asymptomatic radiologic abnormalities, hypertension due to kidney disease)	albuminuria proteinuria hematuria	♦diagnosis and treatment ♦treatment of comorbid conditions ♦slowing progression ♦cardiovascular disease risk reduction
2	kidney damage with mild ↓ GFR	**60-89**	mild complications	albuminuria proteinuria hematuria	♦estimating progression
3	moderate ↓ GFR	**30-59**	moderate complications	chronic renal failure, early renal insufficiency	♦evaluating and treating complications
4	Severe ↓ GFR	**15-29**	severe complications	chronic renal failure, advanced renal insufficiency, pre-ESRD (end-stage renal disease)	♦preparation for renal replacement therapy
5	Kidney failure	**<15 or dialysis**	uremia, cardiovascular disease (CVD)	renal failure, uremia, ESRD	♦renal replacement (if uremia present)

STAGES 1-4 of CKD→ conservative management

identify and treat prerenal and postrenal factors

restrict diet protein (0.8 g/kg/day) – protection of remaining nephrons

aim of urine flow rate of 1500-2000 ml/day

iron is the most likely to require supplementation

adjust dietary sodium/potassium (severe restriction unnecessary except oliguria)

treat acidosis with sodium bicarbonate

control blood pressure (diet and diuretics)

restrict dietary phosphate (give phosphate binders, calcium supplements and consider vitamin D

STAGE 5 of CKD → dialysis treatment (see below)

Creatinine serum concentration is increased (>1.2 mg/dl) only when GFR ranges between 59 and 15 ml/min/1.73 m^2 (in stages 3 –5 of CKD)

Uremia (uremic syndrome) – stage 5 of CKD

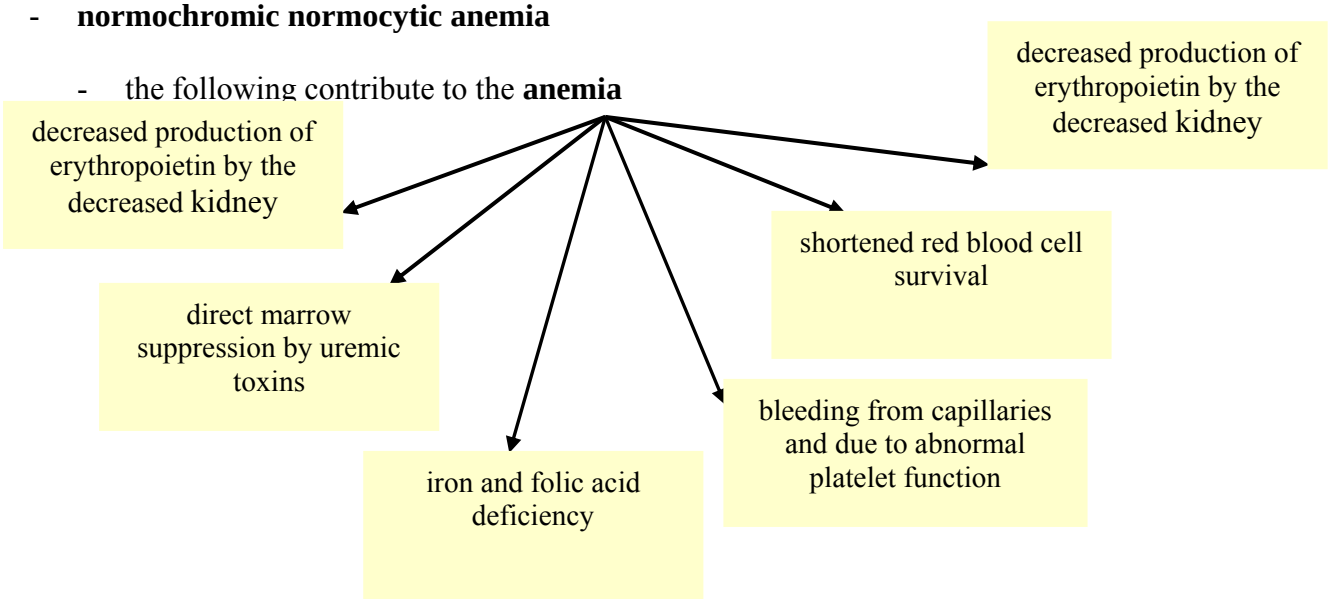
- it is a group of symptoms and signs, some or all are found in patients with serious reduction of excretory capacity (i.e. GFR), from any cause
- it rarely manifests itself clinically until the GFR has fallen to 20% of normal value or less
- symptoms and signs of uremic syndrome results (mainly) from toxic accumulation of waste products, depletion of essential compounds and failure of biosynthetic function of kidneys:
- biochemical features:
  - usually GFR < 10 (15) ml/min
  - usually serum creatinine > 8(12) mg/dl
  - usually BUN > (60) 100 mg/dl

•**nervous system**: fatigue, malaise, depression, involuntary movements, nausea, fits, coma, priuritius, paraesthesiae, neuropathy
•**cardiopulmonary**: pericarditis, pleurisy, dyspnoea, Kussmaul brething
•**dermatological**: priuritus, purpura, pallor, pigmentation, urea frost
•**gastrointerstinal**: anorexia, nausea, vomiting, GI bleeding, constipation, diarrhoea, peptic ulceration, angiodysplasia, colitis, foetor
•**hematological**: anemia (normochromic, normocytic), bleeding (disordered platelet function)

♦**uraemic toxins** (PTH, gastrin, glucagon, calcitonin, purine metabolites, aliphatic and aromatic amines, phenols and indoles (so-called 'middle molecules' – compounds of molecular weight 500-5000 Da)

Haematopoietic system in uremia

- **normochromic normocytic anemia**
  - the following contribute to the **anemia**



- **coagulation abnormalities**

  - qualitative defect in platelet function and abnormal factor VIII function
  - serum concentration of various proteins of coagulation cascade usually within normal limits
  - plasma fibrinogen levels may be increased

- think about anemia diagnosis if:

  - **HCT below 33%**, **HGB below 11 g/dl** – (females before menopause and all sex before maturity)

  - **HCT below 37%**, **HGB below 12 g/dl** – (adult male, post-menopausal female)

- anemia assessment – before starting rHuEPO (recombinant human erytrhropoietin) treatment:

  •HCT, HGB, RBC

  •reticulocyte count

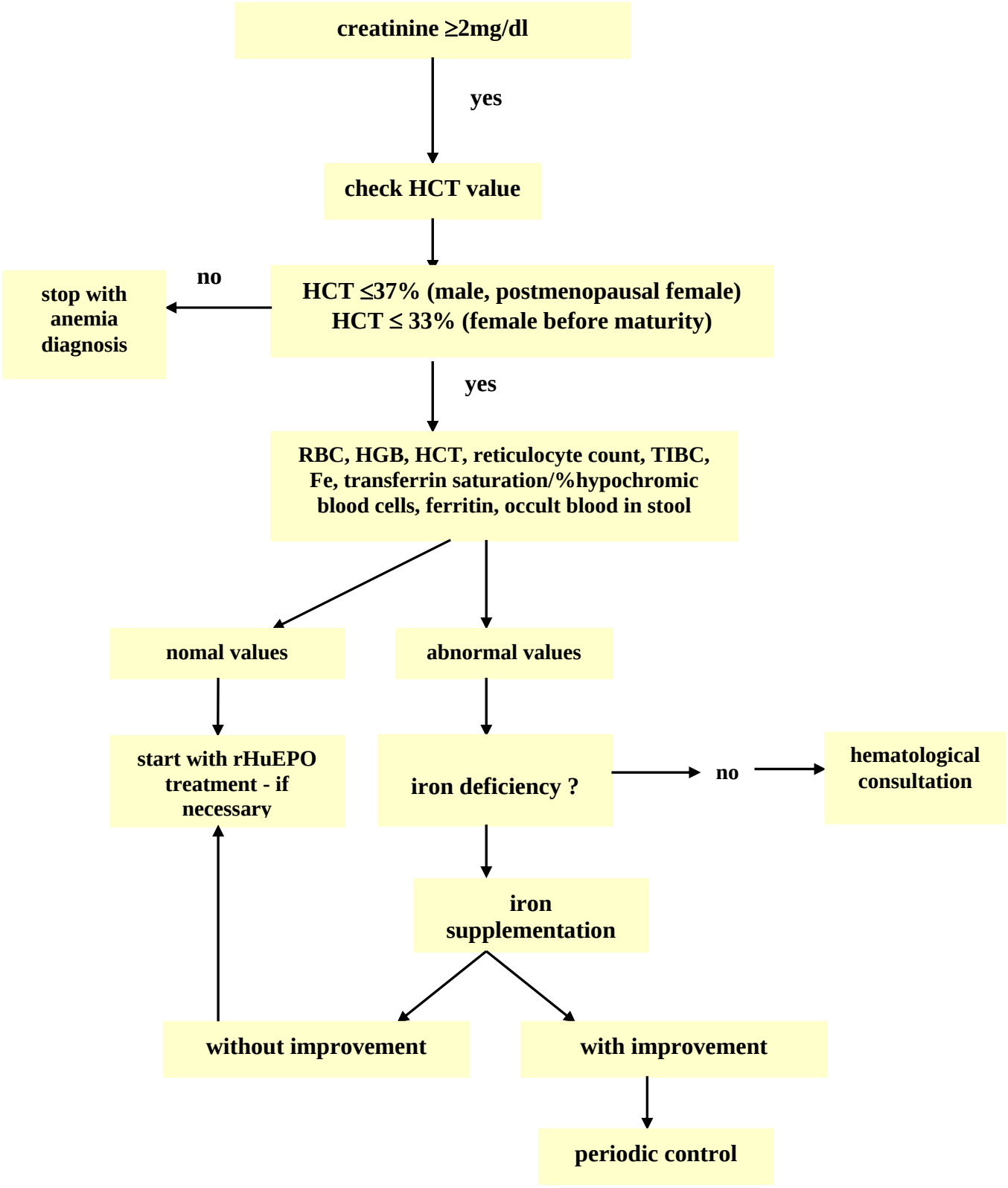
  •iron metabolism parameters:
  - serum iron concentration
  - serum ferritin concentration
  - transferrin saturation

- **the correct values of selected hematological variables during rHuEPO treatment:**

•HCT	**33 - 36%**
•HGB	**11 – 12 g/dl**
•transferrin saturation	**≥20%**
•serum ferritin concentration	**≥100 ng/ml**
•% hypochromic blood cells	**<10%**

- **iron deficiency is diagnosed**
  if transferrin saturation is below 20% and serum ferritin concentration bellow 100 ng/dl

ANEMIA DIAGNOSIS IN PATIENTS WITH CKD



Cardiovascular system in uremia

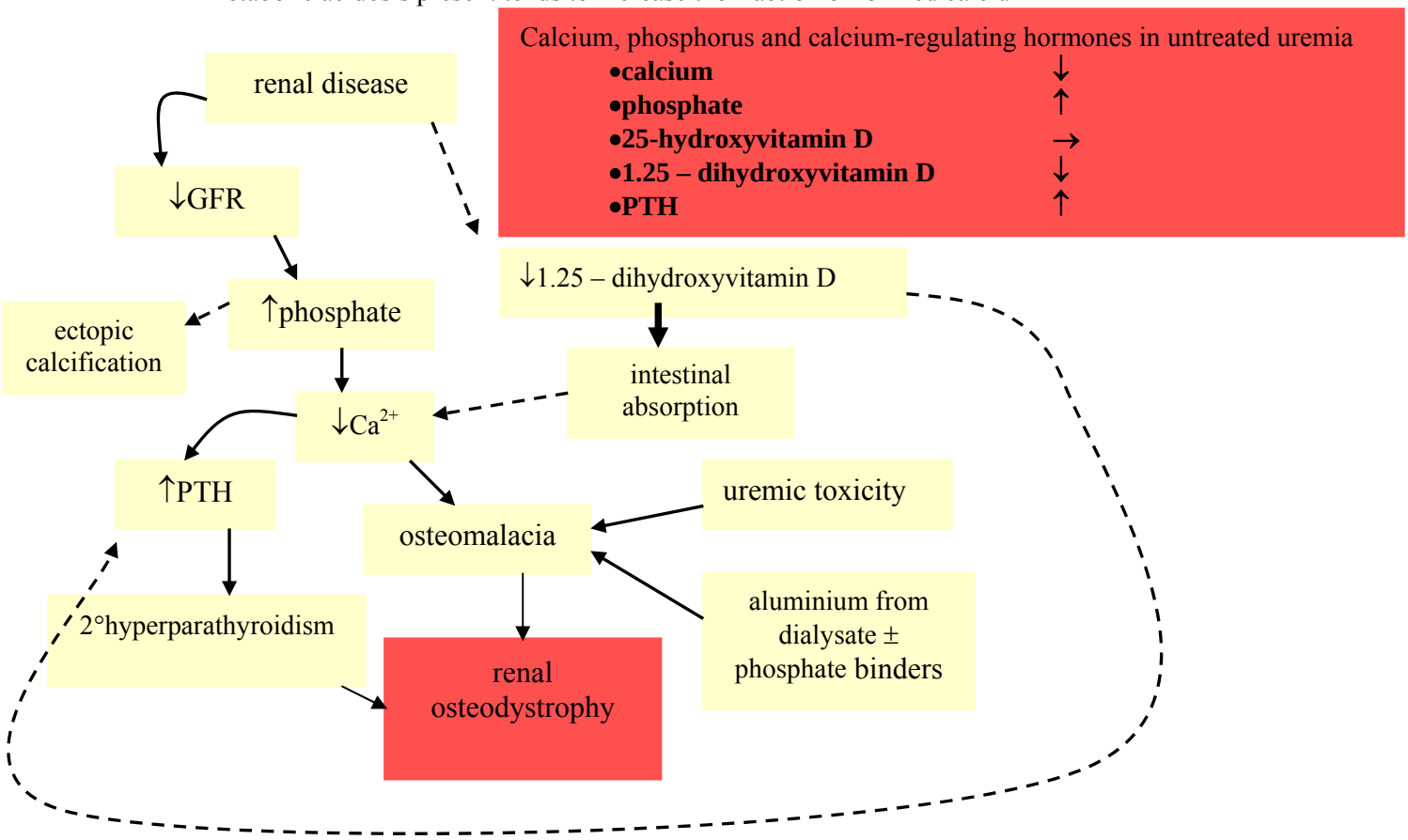
- the most common cause of death in patient with renal failure, regardless of whether they are treated by hemodialysis, peritoneal dialysis or transplantation

Skeletal and mineral metabolism in uremia

Hyperphosphatemia due to marked decrease in GFR
Hypocalcemia secondary to:

- hyperphosphatemia – phosphate retention – a consequence of decreasing filtered load of phosphate
- decreased ability of PTH to mobilize calcium from bone
- decreased serum levels of $1,25(OH)_3$vit. D_3
- decreased calcium absorption from gastrointestinal tract

metabolic acidosis present tends to increase the fraction of ionized calcium



operative in all grades of CRF

operative in moderate and severe CRF (3-5 stages)

Acid-base balance :

- hydrogen ion synthesis **increased**
- hydrogen ion excretion **decreased**

Two types of acidosis in CKD:

- hyperchloremic acidosis
- metabolic acidosis

Metabolic alteration

- disorders of **nitrogen** metabolism- **hipoproteinemia**
  - protein intake **decreased**
  - protein catabolism **incresased**
  - protein losses **incresased**

- disorders of **carbohydrate** metabolism
  - in fasting state **glucose normal or slightly elevated**
  - after oral or intravenous administration of glucose loads **carbohydrate tolerance is impaired (mild)**

  - factors responsible for these abnormalities:
    - resistance of sceletal muscle to insulin
    - increased gluconeogenesis
    - increased hepatic glucose release
    - tendency of uremia per se to inhibit insulin secretion

- disorders of **lipid** metabolism
- plasma cholesterol level **normal**
- plasma triglycerides and VLDL level **elevated**
- plasma HDL and LDL **decreased**

♦ **Magnesium** **normal or elevated**
- serum magnesium level rises in response to acidosis, tissue trauma, administration of vit. D or antiacids containing magnesium

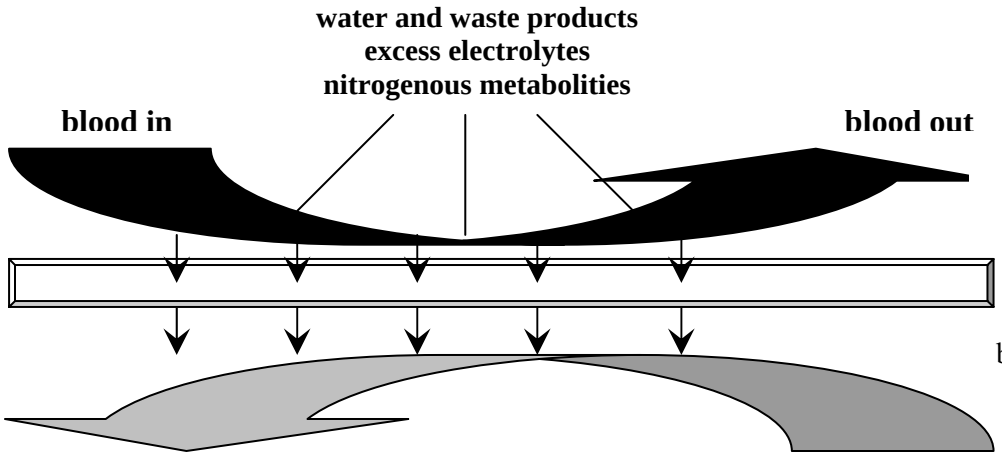
♦ **Potassium excretion**
- increase in potasium excretion per nephron
- increase in potasium excretion per intestine

Hyperkaliemia observed in CKD may be due to:
-acidosis
-β- blockers
-ACE-I administration
-oliguria
-increase in potassium intake

CLINICAL BASICS OF HEMODIALYSIS

Physical principles of dialysis treatment

Hemodialysis (HD)



synthetic semipermeable membrane, through which blood passes at about 300 ml/minute before being returned to the patient

the chemical composition of the dialysate is similar to that of ECF

- urea (so-called 'small molecule'), and other waste products (so-called 'middle molecule'(see above)), which are present only in plasma, diffuse down a concentration gradient across the membrane into the dialysate

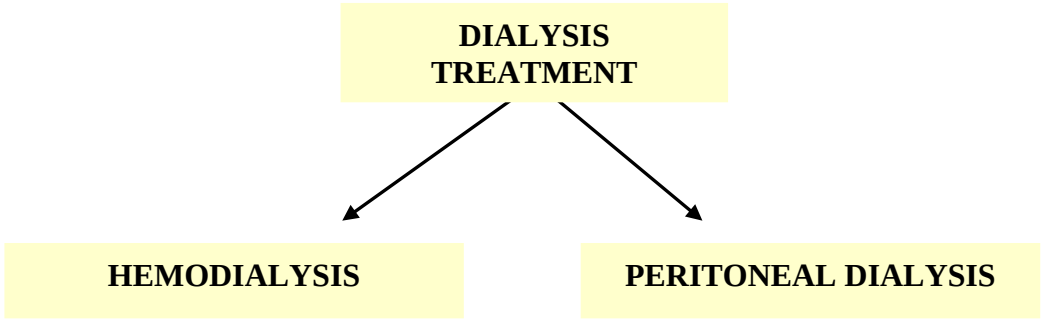
- changes in the composition of the dialysate and in the hydrostatic pressure gradient across the membrane allow "tailoring" of the rate of removal of a variety of substances according to the patient's needs

- adequate access to the circulation is a prerequisite – percutaneous placement of largebore central venous catheters (short-term treatment only), or by creation of arteriovenous fistula (usually at the wrist), thus increasing forearm blood flow and allowing large-bore needles to be placed in forearm veins (long-term treatment)

- treatment is intermittent, typically three sessions of 4 hours each per week

Peritoneal dialysis

- the dialysate is fed into peritoneal cavity via a flexible tube, and the peritoneum itself acts as a semi-permeable membrane
- the dialysate is replaced with fresh fluid when chemical equilibrium is reached
- it usually takes the form of continuous ambulatory peritoneal dialysis (CAPD) in which 2-litre exchanges are performed four times a day
- the technique is simple to learn and the vas majority of patients can carry out and supervise their own treatment at home



INDICATIONS FOR DIALYSIS TREATMENT

1. ***UREMIC SYNDROME:***
   - ***neurological:*** *coma, stupor, fatigue, abnormal mentation, fits, myoclonus, asterixis, peripheral neuropathy*
   - ***cardiovascular/pulmonary:*** *pericarditis, pleurisy, volume overload unresponsive to conservative measures*
   - ***skin:*** *pruritus*
   - ***gastrointestinal:*** *anorexia, nausea, vomiting, unremitting diarrhoea*
   - ***metabolic:*** *unremitting acidosis*

2. ***CHEMISTRY***
   - ***plasma urea more than 100-150 mg/dl***
   - ***severe symptomatic metabolic acidosis (HCO3-<13 mmol/l, pH<7.2)***
   - ***hyperkalemia (potassium concentration >6.5 mmol/l)***
   - ***creatinine clearence <10-12 ml/min***
   - ***serum creatinine > 9 mg/dl, and*** *if CKD is caused by diabetic nephropathy* ***>5 mg/dl***

3. ***SEVERE HYPOVOLAEMIA WITH HYPERTENSION AND/OR PULMONARY OEDEMA***

3. ***THE NEED TO REMOVE FLUID*** *to allow intensive feeding with high energy/high nitrogen diets or total parenteral nutrition*

The optimum time to convert patient with CKD from conservative management to dialysis is judged clinical decision and is reached just before the development of uremic complications

Contraindications to dialysis treatment (especially in case of long-term treatment)

- malignant neoplastic diseases with metastases
- deep mental handicap

Limitations of dialysis treatment

1. The *average* clearence of urea or creatinine achieved by hemodialysis (12 hours treatment per week) is only 6 ml/minute, and by CAPD 7 ml/minute, compared with approx.100-120 ml/minute by normal kidneys.

2. The permeability characteristics of the artificial membrane in HD and, the peritoneum CAPD are inferior to those of the physiological glomerular sieve.

3. Dialysis has no equivalent of 'tubular action'; the dialysis membrane should be permeable enough to allow waste products to cross and not so permeable that excess loss of physiologically important compounds – in practice, the membrane fails on both counts

4. The dialysis has essentially no adaptive capability.

5. Endocrine functions of the kidney are not provided by dialysis. The anemia (erythropoietin) and osteodystrophy (1.25 dihydroxyvitamin D) continue.

Minimal spectrum of assessed parameters during one-year period of HD treatment

- **HCT**	**once a week-once a month**
- **sodium, potassium**	
- **Ca2+, phosphate**	**once a week**
- **blood cell count**	
- **serum urea (before and 30 minutes after HD)**	**once a month**
- **glucose**	
GOT, GPT	
- **lipids**	
- **proteinogram**	
- **coagulogram**	**4 times a year**
- **HBs, anty-HBs, HCV, HIV**	
- **bilirubin**	
- **CRP**	
- **ferritin**	
- **PTH**	**twice a year**
- **chest X-ray**	
- **urine culture**	**once a year**
- **densitometry**	

Clinical enzymology and liver function disorders

Miłosława Zowczak-Drabarczyk MD

Serum aminotransferases

Alanine aminotransferase **(ALT)**:

- is an enzyme **predominantly found in liver** (significant amounts are also present in kidney, with lesser amounts in heart and skeletal muscle),
- is **exclusively cytoplasmic**.

Aspartate aminotranferase **(AST):**

- is an enzyme primarily found in **heart, liver, skeletal muscle, kidney and RBCs**,
- both **mitochondrial (60-80%)** and **cytoplasmatic (20-40%) forms** of AST are found in all cells

approximately 80% of AST in hepatocytes appears to be located in mitochondrial membrane

Factors affecting AST and ALT activity, other than liver injury:

factor	AST	ALT	comments
Time of day		45% variation during day, highest in afternoon, lowest at night	Similar in liver disease and health
Day-to-day	5-10% variation from one day to next	10-30% variation from one day to next	Similar in liver disease and health
Race/gender	15% higher in African-American men		
BMI	40-50% higher with high BMI	40-50% higher with high BMI	Direct relationship between weight and AST,ALT
exercise	Threefold increase with strenuous exercise	20% lower in those who exercise at usual levels than in those who do not exercise or exercise more strenuously than usual	Effect of exercise seen predominantly in men; minimal differences in women(<10%), enzymes increase more with strength training
Hemolysis, hemolytic anemia	Significant increase	Moderate increase attributable to release from red cell	Dependent on degree of hemolysis, usually severalfold lower than increases in LDH
Muscle injury	Significant increase	Moderate increase	Related to amount of increase in CK
Renal failure	Significantly lower	Significantly lower	

- **ALT** has been **used** predominantly to help **confirm liver origin of an AST increase**.
- **ALT** is more specific for **detecting liver disease in nonalcoholic, asymptomatic patients**
- **Pyridoxine deficiency**, common in **alcoholic**s, **decreases** hepatic **ALT** activity

- Patients who chronically abuse alcohol, regardless of the extent of their underlying liver disease, had more consistent mitochondrial AST elevations than other patients (alcohol induces release of mitochondrial AST); values dropped more than 50% in abstinence for more than one week.
- AST is used for monitoring therapy with potentially hepatotoxic drugs

- ***ALT and AST increase 10 times the upper reference limit***, or more, in ***acute viral hepatitis***
- Chronic elevation of ALT/AST in asymptomatic patients may have several causes including alcohol or medication use, chronic viral hepatitis, primary hemochromatosis or nonalcoholic fatty liver disease.
- ***ALT*** is constantly ***higher than AST*** with all causes of acute and chronic ***hepatocellular injury*** (AST/ALT ratio<1) ***with exception of alcoholic*** liver injury and ***liver cirrhosis*** (AST/ALT>1)

Alkaline phosphatase (ALP)

- Is found (in decreasing order of abundance) in **placenta,** ileal mucosa, kidney, **bone and liver**. The bulk of serum ALP of normal patients is made up of liver and bone ALP.
- **ALP** in the liver exists predominantly **in the biliary tract** and is therefore a **marker for biliary dysfunction**
- Cholestasis stimulates synthesis of ALP and release from cell membranes
- The three liver conditions most frequently associated with **ALP elevation** are: **extrahepatic** (common bile duct) **biliary tract obstruction, intrahepatic biliary tract obstruction** due to acute liver injury**,** and **liver space-occupying lesions** (e.g. tumor, abscess, granuloma).
- **Common bile duct obstruction**, **metastatic tumor to the liver**, and uncommon condition of **primary biliary cirrhosis** are the most frequent etiologies for persistent **ALP elevation more than three times** upper reference limit.
- Elevation less than three times the upper limit is some evidence against complete extrahepatic obstruction.

Factors affecting ALP activity, other than liver injury

factor	change	comments
Day-to-day	5-10%	Similar in liver disease and health
Food ingestion	Increases as much as 30 IU/L	Attributable to intestinal isoenzyme
Race/gender	10-15% higher in African-American women and men	
BMI	25% higher with increased BMI	
pregnancy	Increases up to two- to three-fold in third trimester	Attributable to placental isoenzyme
smoking	10% higher	
Oral contraceptives	20% lower	
other	High in bone disease, tumors producing ALP	Can be separated from liver causes by ALP isoenzymes and/or normal GGT

Gamma-glutamyl transferase (GGT)

- GGT enzyme is located mainly in liver cell membranes.
- **GGT activity in serum** comes predominantly from **liver**
- **GGT** is affected by both acute **liver cell damage** and **biliary tract obstruction**.
- Its major use is to discriminate the source of elevated ALP (i.e., **if ALP is elevated**, **measurement of GGT activity is a good indicator of liver source <u>but does not rule out coexisting bone disease</u>**).
- **GGT** is **increased** an average of **10-12-fold** above the upper reference limit in **cholestasis**
- GGT appears to increase in cholestasis by the same mechanisms as does ALP
- **GGT** is **often increased in alcoholics** (70-80%) even without liver disease, in some obese people, in the presence of high concentrations of therapeutic drugs such as **acetaminophen**, and even in the absence of any apparent liver injury.

Factors affecting GGT, other than liver injury

factor	change	comments
Day-to-day	10-15%	Similar in liver disease and health
race	Approximately double in African Americans	
BMI	25% higher with mild increase in BMI; 50% higher with BMI>30	
Food ingestion	Decreases after meals	
drugs	Increased by furosemide, heparin, methotrexate, phenobarbital, phenytoin, carbamazepine, oral contraceptives	Values up to 2 times reference limits are common, may be up to 5 times, especially with phenytoin
smoking	10% higher with 1 pack/day; approximately double with heavier smoking	
other	Patients with DM, hyperthyroidism, rheumatoid arthritis and obstructive pulmonary disease often have increased GGT activity	The reasons are largely obscure
Alcohol consumption	Direct relationship between alcohol intake and GGT	May remain increased for weeks after cessation of chronic alcohol intake

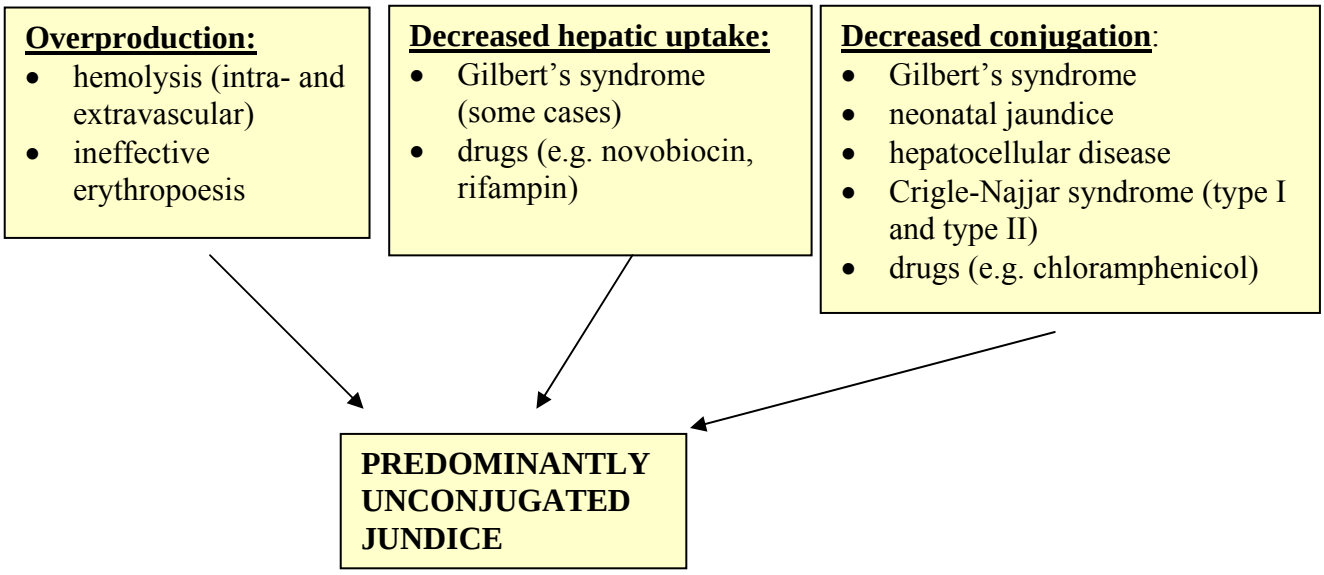
Lactate dehydrogenase (LD)

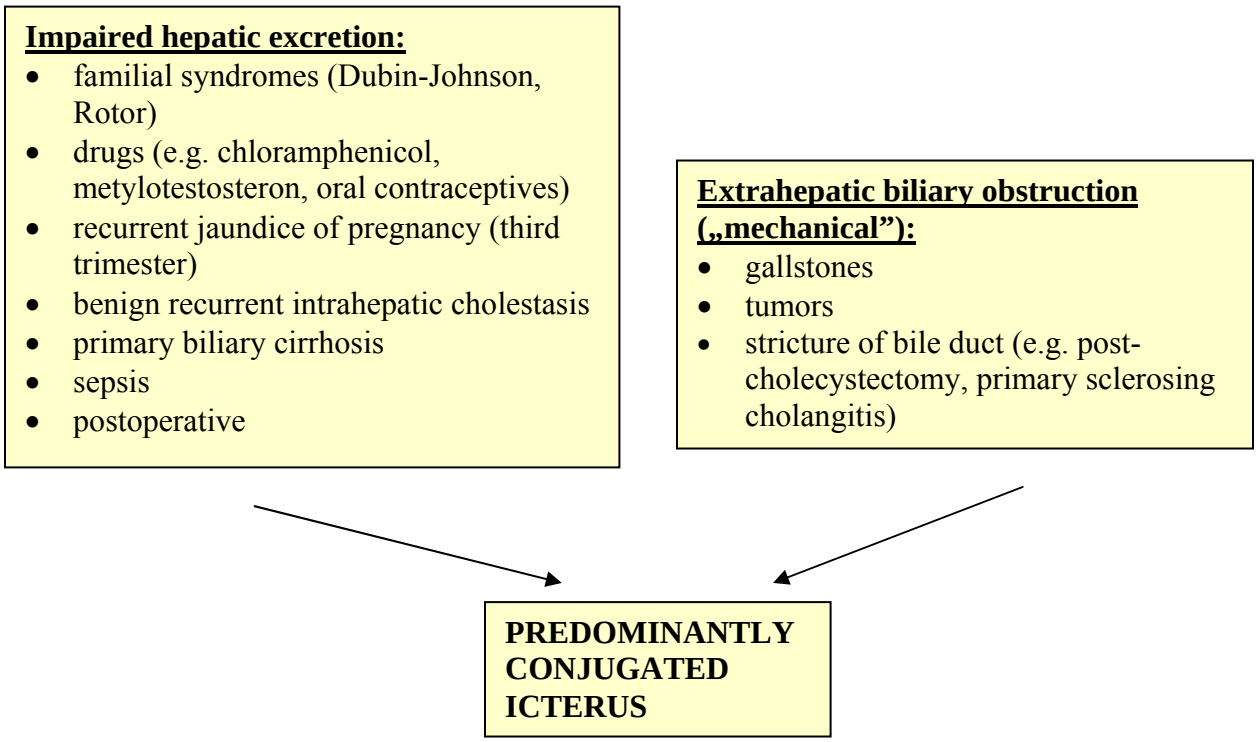
- LD can be fractionated into five isoenzymes using various methods (e.g. electrophoresis).
- **LD5 is** found predominantly **in liver and skeletal muscle**.
- Total LD activity is significantly elevated in acute hepatocellular damage (e.g. hepatitis).
- the **large increase of total LD to levels of 500 IU/L** or more **combined with an increase in alkaline phosphatase (ALP) to levels above 250 IU/L** in the absence of other dramatic abnormalities in other liver function enzyme levels indicates space-occupying lesions of the liver, most often **metastatic carcinoma**

Lipoprotein LpX:

- **Lp X** is a normal **component of bile**,
- its **presence in serum** is an abnormal finding and indicates **obstructive biliary disease**,
- one possible explanation for the origin of LpX is regurgitation of biliary lipids.

Classification of jaundice





Most suitable laboratory markers of liver disorders

HEPATOCELLUCAR INJURY:
- AST and ALT
- bilirubin in serum
- urobilinogen in urine
- serum albumin
- prothrombin time
- GGT,
- LDH
- Viral Ab/Ag

BILIARY OBSTRUCTION:
- ALP
- GGT
- bilirubin in serum
- bilirubin in urine
- Lp X
- 5'-Nucleotidase

TOXIC INJURY e.g. ALCOHOL, DRUGS:
- AST
- GGT

Hemochromatosis

- An increase in the quantity of iron storage in the body is called ***hemosiderosis*** (e.g. alcoholic liver disease, chronic HCV infection, non-alcoholic steatohepatitis).
- ***Hemochromatosis(ph)*** is an increase in total body iron stores with iron deposition in parenchymal tissues that ultimately leads to functional impairment of most severely affected organs: liver→cirrhosis, pancreas→diabetes mellitus, heart→cardiomyopathy, joints→arthritis, etc.
- Signs and symptoms of ph usually develop between the ages of 40 and 60.

Hemochromatosis:

→ **acquired**- exogenous iron overload due to repeated blood transfusions or excessive dietary iron ingestion)

→ **hereditary, primary** (ph)- frequent genetic disorder (1/200- 1/400) and the most frequent metabolic liver disease with multisystem involvement.

First-line screening tests:
- ***percent of transferrin saturation*** **and**
- ***serum ferritin concentration***

Definitive tests:
- ***genetic testing*** (autosomal recessive trait: C282Y mutation of the HFE gene in over 90% of ph cases) and
  - ***liver biopsy*** but ***magnetic resonance imaging*** can also be alternatively used to estimate liver iron content

Iron indices in normal subjects and in patients with symptomatic hemochromatosis:

	Normal	Symptomatic hemochromatosis:
Plasma iron (ug/dL)	50-150	180-300
Total iron binding capacity (ug/dL) TIBC	250-375	200-300
Percent of transferrin saturation	20-40	50-100
Serum ferritin (ng/mL)	10-200	400-6000
Urinary iron after 0,5 gm desferrioxamine	0-2	9-23
Liver iron (ug/100mg dry weight)	30-140	600-1800

References

1. Cecil Essentials of Medicine. 3rd.ed. W.B. Saunders Company. Philadelphia 1993.
2. Harrison's Principles of Internal Medicine. 16th ed. McGraw-Hill Health Professions Division. 2004.
3. Henry J.B. Clinical Diagnosis and Management by Laboratory Methods. 20th ed. W.B. Saunders Company. Philadelphia 2001.
4. Dominiczak M.H. Seminars in Clinical Biochemistry
5. Ravel R. Clinical Laboratory Medicine. Clinical Application of Laboratory Data. 6th ed. Mosby-Year Book. 1995.
6. Dufor R.D., Lott J.A., Nolte F.S., Gretch D.R., Koff R.S., Seeff L.B. Diagnosis and monitoring of hepatic injury.I. Performance characteristics of laboratory tests. Clinical Chemistry 2000, 46: 2027-2049.
7. Dufor R.D., Lott J.A., Nolte F.S., Gretch D.R., Koff R.S., Seeff L.B. Diagnosis and monitoring of hepatic injury.II. Recommendations for use of laboratory tests in screening, diagnosis, and monitoring. Clinical Chemistry 2000, 46: 2050-2068.

The application of laboratory methods in the diagnosis and management of ischemic heart disease

Hanna Kara-Perz MD

Myocardial ischemia

Ischemia refers to lack of oxygen due to inadequate perfusion, which results from an imbalance between oxygen supply and demand.

Causes of myocardial ischemia:

Atherosclerotic obstructive coronary artery disease
Collagen vascular disease
Congenital coronary artery anomalies
Hereditary disorders
Dissection
Coronary artery embolism
"Functional causes" in the absence of anatomic coronary artery disease
- increased myocardial oxygen demand
- decreased myocardial oxygen supply

Some factors that influence myocardial metabolism

Oxygen demand	Oxygen supply
-heart rate	-oxygen content of the blood
-afterload	-volume of blood flowing
-contractility	through the coronary arteries
-wall tension	per unit of time

Coronary artery disease (CAD)

Stable angina pectoris
Unstable angina pectoris

- new onset (<2 months) angina that is severe and/or frequent (>= 3 episodes per day)
- accelerated angina
- angina at rest (with pain lasting more than 20 min)
- variant angina (episodic focal spasm of coronary artery)
- non-Q myocardial infarction
- unstable angina post MI (after more than 24 h after MI)

The diagnosis is made on the basis of the medical history, ST-segment changes, and absence of increased serum cardiac markers.

Standard laboratory test
Lipid profile and carbohydrate tolerance should be considered in patients with CAD

Myocardial infarction (MI)

MI generally occurs when there is abrupt decrease in coronary blood flow following a thrombotic occlusion of coronary artery previously narrowed by atherosclerosis

Clinical presentation

- **frequency** is **highest in the morning** within a few hours of awaking
- **pain** is the most common presenting complaint (features of pain: heavy squeezing, crushing, stabbing, burning)

- pain is often accompanied by weakness, sweating, nausea, vomiting, anxiety, and sense of impending doom
- pain of MI can simulate pain from acute pericarditis, pulmonary embolism, acute aortic dissection, costochondritis
- **SBP** usually declines 10-15 mmHg from the preinfarction state

Typical serum cardiac markers

Creatine kinase (CK)

- Composed of two **subunits: B (brain)** and **M (muscle)**
- **3 isoenzymes:** (localized in cytoplasm, or connected to myofibrils)

  CK-BB (CK-1) – brain, prostate, intestine, lungs
  CK-MB (CK-2)- heart, skeletal muscle
  CK-MM (CK-3)- skeletal muscle, heart

CK-Mt - isoenzyme localized in mitochondria

- **macromolecular forms of CK**
  makro CK-type 1 has been identified to be CK-BB linked with IgG
  makro CK-type 2 has been identified as CK-Mt oligomer

- **CK isoforms**
  Subunits B and M contain lysine on the C-end, but only the M subunit may be hydrolyzed by carboxypeptidase in blood
  $CK\text{-}3_2$, $CK\text{-}3_1$, $CK\text{-}2_1$- serum isoforms
  $CK\text{-}3_3$, $CK\text{-}2_2$- tissue isoforms (genetically determined)

Creatine kinase activity

Increased CK activity is also observed in:

- skeletal muscle disorders (including damage secondary to trauma, **intramuscular injections**!, prolonged immobilization, surgery)
- after physical effort
- after electric cardioversion, cardiac catheterization
- hypothyreosis

CK-MB activity

Enzyme	Activity [IU/L]	Increase	Onset of increase	Peak value	Return to the normal range
CK-MB	**25**	**2-10 x**	**4-8 h**	**1-2 day**	**2-3(4) day**

- ”gold standard”
- **specificity** is very high, but not 100%
- activity may be increased in:
  skeletal muscle diseases
  renal failure
  some neoplasms

- **CK-MB index = CK-MB act/CK act x 100%**

We calculate this index to increase specificity as for myocardium

- **Diagnostic sensitivity**

30% in the 4^{th} h from the first symptoms

- **Subsequent measurement** of CK-MB activity increases both sensitivity and specificity

CK-MB mass

- Evaluation of CK-MB mass should replace CK-MB activity

onset	4 (3,5-5,5) h
peak value	14 (11,5-15,5) h
decrease to normal range	87 (68-96) h

CK-MB mass **is not useful in late stage of MI**, because increased results may be observed only for about 30 h

- **specificity**- very high, but not 100%
  CK-MB mass may be increased in:
  skeletal muscle diseases

- **diagnostic sensitivity**

in the 4th h of MI - 50%
after 6 h -75%
after 8 h -90%

- CK-MB mass has **great effectiveness in excluding of MI** (when there is no increase of CK-MB mass within 8 h from the first stenocardial symptoms it allows to exclude MI in 93-95%)
- CK-MB mass is **useful in evaluation of effectiveness of fibrinolytic therapy**

Myoglobin

- The first serum cardiac marker that rises above the normal range after MI (early diagnosis of MI)

onset	**3,3 (2,5-4,3) h**
peak value	**6,0 (4,0-8,5) h**
decrease to normal range	**20 (15,5-39,9) h**

Myoglobin **is not useful in late stage of MI**, because increased results may be observed only for about
12-15 h

- **specificity**- lack of cardiac specificity
- Myoglobin conc. may be increased in:
  -skeletal muscle diseases and injury
  -renal failure
  -after physical effort

Evaluation of myoglobin should be connected with evaluation of the other cardiac-specific markers

- **diagnostic sensitivity**

after 2,5 h after the first symptoms of MI – 30%
in the 4th h of MI- 50%

- Myoglobin has **great effectiveness in excluding of MI** (when there is no increase of myoglobin within
  4 h from the first stenocardial symptoms it allows to
  exclude MI in 90-100%)
- Myoglobin is **useful in evaluation of effectiveness of fibrinolytic therapy**

Troponin

Troponin is a protein complex located on the thin filament of striated muscles and consists of three isotypes:

Troponin T (TnT)- binds the troponin complex to tropomyosin

Troponin I (TnI)- functions to inhibit actomyosin ATP-ase

Troponin C (TnC)- regulates TnI activity by binding calcium

TnI and TnT have diagnostic value in the MI

TnI and TnT occur in 3 isoforms:

a) cardiac isoform (cTnI and cTnT)
b) fast myofibril isoform
c) slow myofibril isoform

		TnI	TnT
onset	-	4,5 (4-6,5) h	5,0 (3,5-8,1) h
peak value	-	19,0 (12,8-29,8) h	18,0(12,8-75,0)h
decrease to normal range	-	168,0 (105-168) h	172 (147-296) h

- **specificity to myocardium**
  -cTnI reveals **absolute** specificity to myocardium

  -cTnT high, but not 100% specificity to myocardium

  *increased value of cTnT may be observed in:

  chronic renal failure

  muscular dystrophy

  polymyositis

- **diagnostic sensitivity**
  -after 4 h from the first symptoms of MI- 50%

  -after 6 h from the first symptoms of MI- 70%

- measurement of TnT and TnI is **useful in evaluation of minor myocardial injury** (two cut-off values)

- measurement of TnT and TnI is **useful in evaluation of risk of complications of unstable angina pectoris**

Myocardial infarction – cardiac markers

*** early diagnosis**
- **MYOGLOBIN**
- **CK-MB isoforms**

*** definitive diagnosis**
- **CK-MB**
- **TROPONIN**

*** late diagnosis**
- **TROPONIN**
- **LDH**

Brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)

I. BNP and NT-proBNP **production** within the heart ventricles as a result of increased pressure and diastolic overload

II. Main **effects** of BNP and NT-proBNP

a) reduction of blood pressure by arterial and venous vasodilatation
b) natriuretic and diuretic effects by increasing GFR and decreasing sodium reabsorption within the nephrons
c) inhibition of sympathetic system and renin-angiotensin-aldosterone system

III. Significance of BNP and NT-proBNP evaluations in **congestive heart failure (CHF)**

a) **diagnostic** value (threshold value - 80 pg/ml, increased levels in CHF)
b) **prognostic** significance (higher values associated with poor prognosis)
c) **therapeutic** value (nesiritid - recombinant human BNP used in decompensated CHF)

IV. Significance of BNP and NT-proBNP evaluations in **acute coronary syndromes (ACS)**

a) diagnostic value (ischaemia induces BNP and NT-proBNP releasing, but the diagnostic importance has not been established so far, according some authors these peptides may be used as a substitutive ischaemic marker)
b) **prognostic** significance (higher levels are associated with increased early/late mortality and progression of heart failure independently of troponin and CRP elevation; this linear correlation is especially observed in NSTEMI, threshold value has not been established)
c) influence on therapeutic strategy (some data indicate beneficial effects after early applying invasive methods among patients with ACS and increased NT-proBNP levels, but it requires further evaluation)

The differential diagnosis of disorders of lipid metabolism

Ewa Wysocka MD

THE MOST IMPORTANT RISK FACTORS FOR THE DEVELOPMENT OF CORONARY HEART DISEASE (CHD)

LIFESTYLE	BIOCHEMICAL AND PHYSIOLOGICAL SIGNS *Submitting modification*	INDIVIDUAL SIGNS *Not submitting modification*
• Diet abounding with saturated fatty acids, cholesterol and calories • Smoking * • Excessive alcohol consumption • Small physical activity	• ↑ serum T-C * (LDL-C) conc. • ↑ serum TG conc. • ↓ serum HDL-C conc. * • ↑ blood pressure* • obesity • hyperglycemia/ diabetes * • prothrombotic factors • ↑ serum homocystein conc.	• age *: man ≥ 45 women ≥ 55 • premature menopause* • early onset of CHD or other artery disease caused by atherosclerosis (familial history)*: in men < 55 yr in women < 65 yr • symptoms of CHD or other artery disease caused by atherosclerosis *

THE RISK CATEGORIES OF CHD'S INCIDENT (1)

MILD RISK
1 or 2 of the mild risk factors

MILD RISK FACTORS

- LDL-C 130-159 mg/dL
  (3,4-4,1 mmol/L)

  T-C : 200-239 mg/dL
  (5,2-6,2 mmol/L)
- Blood pressure :

  SBP 140-159 mmHg
  and/or
  DBP 90-99 mmHg

MODERATE RISK
1 moderate risk factor

MODERATE RISK FACTORS

- smoking
- LDL-C 160-210 mg/dL
  (4,1-5,4 mmol/L)

  T-C : 240-300 mg/dL
  (6,2-7,8 mmol/L)
- HDL-C : men ≤ 35 mg/dL
  (0,9 mmol/L)

  women ≤ 40 mg/dL
  (1,0 mmol/L)
- SBP 160-179 mmHg
  and/or
  DBP 100-109 mmHg
- Age: men ≥ 45
  women ≥ 55
- Premature menopause
- early onset of CHD or other artery diseases caused by atherosclerosis in first-relative:
  men < 55
  women < 65

THE RISK CATEGORIES OF CHD'S INCIDENT (2)

HIGH RISK

- 1 strong risk factor
- 2 moderate risk factors

VERY HIGH RISK

- 1 very strong risk factor at least (especially CHD), or
- 2 strong risk factors at least, or
- 3 moderate risk factors at least

STRONG RISK FACTORS

- smoking 20 or more cigarettes /day
- LDL-C > 210 mg/dL (5,4 mmol/L)
  T-C > 300 mg/dL (7,8 mmol/L)
- SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg

VERY STRONG RISK FACTORS

- CHD already diagnosed
- other artery diseases caused by atherosclerosis, clinically documented
- familial hyperlipoproteinemia
- diabetes mellitus

PRIMARY PREVENTION OF CORONARY HEART DISEASE (1)

1. Estimate the risk factors such as the lifestyle, individual signs, biochemical and physiological signs in person above 20 yr.
2. If one doesn't smoke and doesn't have risk factors such as his individual signs (not submitting modification), and his :

T-C < 230 mg/dL
(6,0 mmo/l)
glucose conc. < 126 mg/dL
(7,0 mmol/L)
blood pressure < 160/100 mmHg

MILD RISK

- information about healthy lifestyle and rational feeding
- the next control for :

  T-C in 5 years
  body weight – in 2 years
  blood pressure (if normal) – in 2 years
- if arterial hypertension is present, obtain BP < 140/90 mmHg
- if overweight is diagnosed, encourage to lose weight.

3. If one has at least one of the following risk factors : smoking, T-C ≥ 230 mg/dL, SBP ≥ 160 mmHg, DBP ≥ 100mmHg, BMI ≥ 30,0 kg/m^2, plasma glucose concentration ≥ 126 mg/dL, CHD or other artery disease caused by atherosclerosis, it is necessary to determine full lipid profile in serum, than estimate the category of general CHD' risk and perform proper proceeding

PRIMARY PREVENTION OF CORONARY HEART DISEASE (2)

MODERATE RISK

- recommend changing of the life style (diet in particular)
- obtain LDL-C < 160 mg/dL
  (4,1 mmol/L)
- obtain TG < 180 mg/dL
- obtain BP < 140/90 mmHg
- if significant overweight or obesity, recommend losing weight about at least 10%.

3. continued

HIGH RISK

- recommend changing of the way of life (diet in particular)
- obtain LDL-C < 130 mg/dL(3,4 mmol/L)
- obtain TG < 180 mg/dL(2,0 mmol/L)
- control BP < 140/90 mmHg
- if significant overweight or obesity, recommend losing weight about at least 10%.

VERY HIGH RISK

- recommend changing of the life style (diet in particular)
- obtain LDL-C < 100 mg/dL (2,6 mmol/L)
- obtain TG < 180 mg/dL (2,0 mmol/L)
- obtain HDL-C > 35 mg/dL (0,9 mmol/L) in men
  > 40 mg/dL (1,0 mmol/L) in women
- control BP < 140/90
- in diabetics : obtain well-controlled glycemia and/or serum LDL-C conc. < 100 mg/dL(2,6 mg/dL), TG conc. < 150 mg/dL (1,7 mmol/L), control BP < 130/85 mmHg
- if significant overweigh or obesity, recommend losing weight at least about 10%.

SECONDARY PREVENTION OF CORONARY HEART DISEASE

RISK FACTORS

- smoking
- lipids

  LDL-C < 100 mg/dl (2,6 mmol/l)

  TG < 180 mg/dl (2,0 mmol/l)

  HDL-C : men > 35 mg/dl, women > 40 mg/dl
- BP control < 140/90 mmHg
- body weigh control
- physical activity
- drugs

RECOMMENDATION

Lipids determination – according to myocardial infarction in 4-6 weeks

(it's possible during first 24 hours of acute coronary incident)

Goals: LDL-C < 100 mg/dL , TG < 180 mg/dL (without drugs)

LDL-C 100-130 mg/dL , TG 180-300 mg/dL

LDL-C >130 mg/dL , TG >300 mg/dL (drugs are necessary)

HYPERHOMOCYSTEINEMIA

mild	**10(16) – 30 µmol/l**
moderate	**30 - 100 µmol/l**
severe	**>100 µmol/l**

HYPERHOMOCYSTEINEMIA - MECHANISM OF DISEASE

The vascular lining has a limited capacity to metabolize homocystein (HCY).

HCY as atherogenic factor

- auto-oxidation of HCY results in the production of :

1. *free radicals*
2. *hydrogen peroxide*
3. *thiolactone of HCY*

} oxidative injury of molecules and cells

↓

LDL-apoB-HCYthiolactone - modifed LDL

- limitation of biological access of NO (EDRF) for endothelial cells → impaired vasodilatation

HCY as prothrombotic factor

- increases V and VII plasma factors activities
- decreases activity of protein C
- promotes the binding of Lp(a) to fibrin
- decreases the thrombomodulin expression
- increases expression of tissue factor
- lowers level of the natural cell surface anticoagulant (heparan sulfate)

CAUSES OF HYPERHOMOCYSTEINEMIA

1. Congenital defects – deficiency of enzymes involved in HCY metabolism.
2. Acquired deficiency of folic acid, vit.B_6, vit.B_{12}.
3. Secondary causes: chronic renal failure
   neoplastic diseases
   hypothyroidism.
4. Drugs and substances:
   antagonized folic acid (methotrexate, phenytoine)
   antagonized vit.B_6 (theophylline, coffee).

APPROACHES TO MANAGEMENT OF THE HYPERHCY-PATIENT

1. Screening for hyperHCY in selected high-risk patients:
   - Familial history of CHD
     (50% of patients with CHD had one or more first-degree relatives with hyperHCY)
   - Thromboembolic disease
   - Hypothyroidism
   - Chronic renal failure
   - Treatment with certain medications
2. Try to change HCY level by diet. Reassessment of the one month diet's results.
3. Verify the possibility of secondary causes (neoplastic disease!).
4. Folic Ac. 400 μg daily.

If HCY level is still elevated:

5. Folic Ac. 1 mg + Vit.B_6 25 mg + Vit.B_{12} 500 mg
   daily.

Secondary dislipoproteinemias (1)

CLINICAL DISORDER	↑ PLASMA LIPOPROTEIN	LIPOPROTEIN TYPE	PROPOSED MECHANISM
DIABETES MELLITUS	VLDL (chylomicrons) LDL	4 (rarely 5) 2a, 2b	• ↑secretion of VLDL • ↓catabolism of VLDL and Chylo due to ↓ LPL act. • glycation and oxidation of LDL
HYPO-THYROIDISM	LDL (IDL)	2a (rarely 3)	• ↓ catabolism of VLDL and IDL
CUSHING'S SYNDROME	LDL (VLDL)	2a or 2b	• ↑ secretion of VLDL with conversion to LDL
ACROMEGALY	VLDL	4	• ↑ secretion of VLDL
ANOREXIA NERVOSA	LDL	2a	• ↓ biliary excretion of CH and bile acids
OVERWEIGHT / OBESITY	VLDL	4	• ↑ secretion of VLDL
ALCOHOL	VLDL (chylomicrons)	4 (rarely 5)	• ↑ secretion of VLDL in individuals genetically predisposed to hyperTAG
ORAL CONTRACEPTIVES	VLDL (chylomicrons)	4 (rarely 5)	• ↑ secretion of VLDL in individuals genetically predisposed to hyperTAG
GLUCOCORTICOIDES	LDL (VLDL)	2a or 2b	• ↑ secretion of VLDL with conversion to LDL

Secondary dislipoproteinemias (2)

CLINICAL DISORDER	↑ PLASMA LIPOPROTEIN	LIPOPROTEIN TYPE	PROPOSED MECHANISM
UREMIA	VLDL	4	• ↓catabolism of VLDL due to reduced LPL activity
NEPHROTIC SYNDROME	LDL VLDL	2a or 2b	• ↓ catabolism of LDL and VLDL (proteinuria)
ACUTE HEPATITIS (non-fulminant)	VLDL	4	• ↓ hepatic secretion of LCAT
HEPATOMA	LDL	2a	• lack of feedback inhibition of hepatic CH synthesis by dietary cholesterol
SEVERE STRESS acute myocardial infarction, extensive burns	VLDL	4	• ↑ secretion and ↓ catabolism of VLDL
SYSTEMIC LUPUS ERYTHEMATOSIS	chylomicrons	1	• presence of IgG or IgM that binds heparin - ↓ LPL activity
MONOCLONAL GAMMAPATIES	chylomicrons IDL VLDL	3 or 4	• presence of IgG or IgM that forms immune complex with chylomicron remnants and/or VLDL - ↓ catabolism of VLDL

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel and Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

Adult Treatment Panel III (ATP III) 2003, *still recommended in 2006*

Total Cholesterol Levels (T-C)	
Less than 200 mg/dl	"Desirable" level that puts you at lower risk for heart disease. A cholesterol level of 200 mg/dL or greater increases your risk.
200 to 239 mg/dl	"Borderline-high"
240 mg/d and above	"High" blood cholesterol. A person with this level has more than twice the risk of heart disease compared to someone whose cholesterol is below 200 mg/dl.

LDL-Cholesterol Levels (LDL-C)	
Less than 100 mg/dl	Optimal
100 to 129 mg/dl	Near Optimal/ Above Optimal
130 to 159 mg/dl	Borderline High
160 to 189 mg/dl	High
190 mg/dl and above	Very High

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel and Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

Adult Treatment Panel III (ATP III) 2003, *still recommended in 2006*

HDL-Cholesterol Levels (HDL-C)	
Less than 40 mg/dl	A major risk factor for heart disease
40 to 59 mg/dl	The higher your HDL, the better
60 mg/dl and above	An HDL of 60 mg/dl and above is considered protective against heart disease

Triglyceride Levels (TG)	
Less than 150 mg/dl	Normal
150 to 199 mg/dl	Borderline-high
200-499 mg/dl	High
500 mg/dl or above	Very High

The diagnosis of hyper- and hypoglycemia

Ewa Wysocka MD

The information presented in the chapel has been updated to the latest recommendation of American Diabetes Association:
Standards of Medical Care in Diabetes. Diabetes Care, vol. 29, suppl.1, January 2006

THE DEFINITION OF DIABETES MELLITUS

Metabolic disease of various etiologies, characterized by:

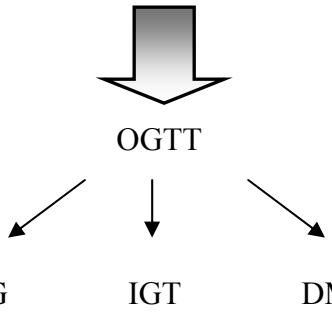
- chronic hyperglycemia with { carbohydrate / lipid / protein } metabolism disorders

  due to an absolute or a relative lack of insulin

- occurrence of the late diabetic complications (microangiopathy, macroangiopathy, neuropathy and cataract).

THE CATEGORIES OF FASTING GLYCEMIA

FASTING GLYCEMIA	NORMAL	BORDERLINE GLUCOSE LEVELS	DIABETES MELLITUS	
VENOUS BLOOD PLASMA	**< 100 mg/dL** *< 5,6 mmol/L*	**100 – 125 mg/dL** *5,6 – 6,95 mmol/L*	**≥ 126 mg/dL** *≥ 7,0 mmol/L*	
WHOLE VENOUS BLOOD	**< 85 mg/dL** *< 4,73 mmol/L*	**85 –109 mg/dL** *4,73 – 6,05 mmol/L*	**≥ 110 mg/dL** *≥ 6,1 mmol/L*	*
WHOLE CAPILLARY BLOOD	**< 85 mg/dL** *< 4,73 mmol/L*	**85 –109 mg/dL** *4,73 – 6,05 mmol/L*	**≥ 110 mg/dL** *≥ 6,1 mmol/L*	*



* Approximately 12 – 18 mg/dL lower concentrations of fasting glucose are observed in whole blood (venous or capillary) comparing with venous blood plasma

ORAL GLUCOSE TOLERANCE TEST
(OGTT)

INDICATIONS	CONTRAINDICATIONS absolute
1. Abnormal (borderline) fasting glycemia; 5,6 mmol/L (100-125 mg/dL).	1. The diagnosis of DM was made.
2. Glucosuria with normal fasting glucose concentration.	2. Some gastrointestinal diseases; malabsorption syndrome, after stomach resection.
3. The diagnostic way of gestational diabetes mellitus (GDM).	**CONTRAINDICATIONS** relative – about 4-6 weeks
4. In persons with high risk of especially type 2 DM, i.e. metabolic syndrome with normal fasting glycemia. It is recommended to perform OGTT every 2 years in obese children and youth.	1. Severe acute states. 2. Long-term physical inactivity.

TEST STANDARDIZATION

1. Patient's diet – approximately 300g of carbohydrates/day for 3 days preceding the test (at least 150g/day).
2. Usual physical activity.
3. Drugs (taking by patients) which can influence blood glucose conc.
4. Smoking is not allowed.
5. In the morning, after 8-14 hours fasting.
6. The oral glucose load:

ADULTS	CHILDREN	PREGNANT WOMEN
75g	1.75g/kg body weight (max.75g)	75g 50 and 100g

- dissolved in 250-300 ml of water
- drinking within 5 minutes.

ORAL GLUCOSE TOLERANCE TEST (75,0g of glucose)
- RESULTS' INTERPRETATIONS

CATEGORY	BLOOD SAMPLES	FASTING GLYCEMIA, AT 0 MIN.	GLYCEMIA AT 120 MIN.
normal values	VENOUS BLOOD PLASMA	**< 100 mg/dL** *< 5,6 mmol/L*	**< 140 mg/dL** *< 7,8 mmol/L*
Impaired Fasting Glycemia, Isolated IFG	VENOUS BLOOD PLASMA	**100 – 125 mg/dL** *5,6 – 6,95 mmol/L*	**< 140 mg/dL** *< 7,8 mmol/L*
Impaired Glucose Tolerance, Isolated IGT	VENOUS BLOOD PLASMA	**< 100 mg/dL** *< 5,6 mmol/L*	**140 –199 mg/dL** *7,8 – 11,05 mmol/L*
IFG & IGT	VENOUS BLOOD PLASMA	**100 – 125 mg/dL** *5,6 – 6,95 mmol/L*	**140 –199 mg/dL** *7,8 – 11,05 mmol/L*
DIABETES MELLITUS	VENOUS BLOOD PLASMA	**< 126 mg/dL** *< 7,0 mmol/L*	**≥ 200 mg/dL** *≥ 11,1 mmol/L*

THE CRITERIA FOR DIAGNOSIS OF DIABETES MELLITUS

1. The classic diabetic symptoms : polyuria, polydipsia and unexplained weight loss

and

a casual plasma glucose conc. (random glycemia) ≥200 mg/dL (11,1 mmol/L)
(casual is defined as any time of day without regard to time since last meal).

2. Fasting plasma glucose (FPG) conc. ≥ 126 mg/dL (7,0 mmol/l) stated twice
(fasting is defined as no caloric intake for at least 8h).

3. Pathological result of OGTT :
a 2-hour postload plasma glucose conc. ≥ 200 mg/dL (11,1 mmol/L).

- In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.
- These diagnostic criteria apply to children as well as adults.
- Pregnant women undergo special diagnostic way.
- The OGTT must be performed according to WHO specifications.

(AMERICAN DIABETES ASSOCIATION, Standards of Medical Care in Diabetes
Diabetes Care, vol. 29, suppl.1, January 2006):

1. The FPG is the preferred test to screen for pre-diabetes and diabetes.
2. The OGTT is not recommended for routine clinical use, but may be required
    - in the evaluation of patients with IFG
    - when diabetes is still suspected despite a normal FPG
    - during the postpartum evaluation of women with GDM.

GESTATIONAL DIABETES MELLITUS (GDM)

(ADA recommendation 2006)

Low risk for GDM

Low-risk status requires no glucose testing, but this category is limited to those women meeting **all of the following** characteristics:

1. Age < 25 yrs.
2. BMI or weight normal before pregnancy.
3. Member of an ethnic group with a low prevalence of GDM.
4. First-degree relative without diabetes.
5. No history of abnormal glucose tolerance.
6. No history of obstetric complications.

Screening OGTT (glucose challenge test – GCT)

- doesn't require an overnight fast
- **50,0g** glucose dose
- blood sample is drawn after 1 hour
- plasma glucose conc.: < 140 mg/dL (7,8 mmol/L) rules out GDM
  ≥ 140 mg/dL (7,8 mmol/L) requires a full diagnostic test.

Diagnostic OGTT

- requires an overnight fast (8-14 hours)
- **100,0g** glucose dose
- blood samples are drawn just before and 1,2,3 hours after
- plasma glucose conc. elevated in at least 2 of 4 samples ⟶ GDM

ORAL GLUCOSE TOLERANCE TEST IN PREGNANT WOMEN

- NORMAL VALUES

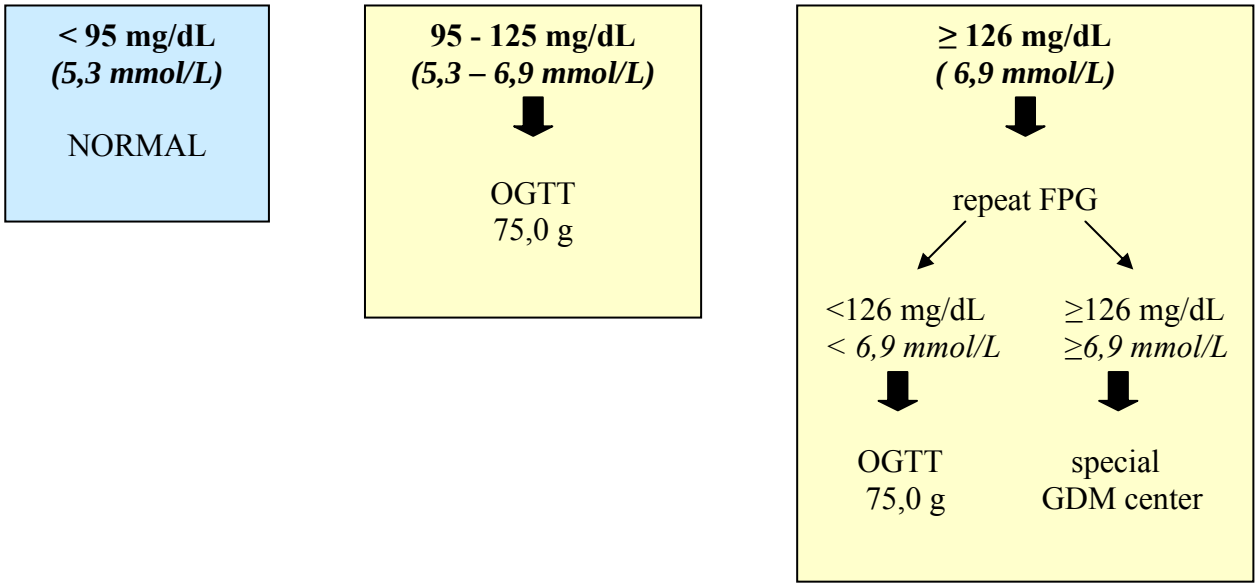
(ADA - 100,0g of glucose)

	FASTING GLYCEMIA	GLYCEMIA AT 60 MIN.	GLYCEMIA AT 120 MIN.	GLYCEMIA AT 180 MIN.
VENOUS BLOOD PLASMA	**< 95 mg/dl** ***< 5,3 mmol/l***	**< 180 mg/dl** ***< 10,0 mmol/l***	**< 155 mg/dl** ***< 8,6 mmol/l***	**< 140mg/dl** ***< 7,8 mmol/l***

THE MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

I. Risk assessment for GDM should be undertaken at the first prenatal visit;

1. Fasting plasma glucose (FPG) concentration:



- Interpretation in compliance with WHO recommendation :

GDM when 120' glycemia is { 140-199 mg/dL (7,8-11,0 mmol/l) or ≥ 200 mg/dL (11,1 mmol/l).

- High-risk women not found to have GDM at the initial screening and average-risk women should be tested between 24 and 28 weeks of gestation.

2. Between 24 and 28 weeks of gestation OGTT should be performed:

A. One-step approach: perform a 75-g OGTT
B. Two-step approach:
   1) an initial screening with glucose challenge test (GCT)
   2) a diagnostic 75-g OGTT.

ADA 2005: "The diagnosis can be made using a 75-g glucose load, but that test is not as well validated for detection of at-risk infants or mothers as the 100-g OGTT."
ADA recommends 100-g OGTT.

II. The consequences of the diagnosed IFG during pregnancy are still unknown.

III. GDM women should be screened for diabetes 6-12 weeks postpartum, to verify diagnosis :

- Approximately 10% of GDM women fulfill criteria for diabetes. They are reclassified as having DM.
- Approximately 5-10% women continue to have abnormal glucose metabolism below diabetic levels. They are reclassified as having IFG or IGT.
- 30% of GDM women become diabetic within the next 5 to 10 years.

THE RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

(Criteria for testing for diabetes – European standards)

1. Obesity (BMI $\geq$ 25 kg/m^2).
2. First-degree relative with diabetes.
3. Habitual physical inactivity.
4. Belonging to a high-risk ethnic or racial group.
5. Previous evidence of impaired glucose homeostasis.
6. GDM in the past history.
7. Having delivered a baby weighing >4,0 kg.
8. Arterial hypertension ($\geq$140/90 mmHg).
9. Dyslipidemia: HDL cholesterol conc. < 40 mg/dl (1,0 mmol/l)
   and/or
   TG conc. $\geq$ 250 mg/dl (2,85 mmol/l)
10. Other clinical states associated with insulin resistance
    (i.e. polycystic ovary or *acanthosis nigricans*).
11. Symptoms of CVD.

Screening for DM should start:

- At **age 45** years and be repeated **every 3 years** in persons without any risk factor
- Earlier and more frequently in those with at least one factor of the above list.

CRITERIA FOR TESTING FOR DIABETES IN ASYMPTOMATIC ADULT INDIVIDUALS

American Diabetes Association 2006

1. Testing for diabetes should be considered in all individuals at age 45 years and above, particularly in those with a BMI ≥25 kg/m^2 * and, if normal, should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight (BMI ≥25 kg/m^2 *) and have additional risk factors, as follows:
   - are habitually physically inactive
   - have a first-degree relative with diabetes
   - are members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - have delivered a baby weighing >9 lb (4,0 kg) or have been diagnosed with GDM
   - are hypertensive (≥140/90 mmHg)
   - have an HDL cholesterol level <35 mg/dl (0.90 mmol/l) and/or a triglyceride level >250mg/dl (2.82 mmol/l)
   - have PCOS (polycystic ovary syndrome)
   - on previous testing, had IGT or IFG
   - have other clinical conditions associated with insulin resistance (acanthosis nigricans)
   - have a history of vascular disease

*May not be correct for all ethnic groups.

TESTING FOR TYPE 2 DIABETES IN CHILDREN - CRITERIA

American Diabetes Association 2006

- **Overweight** (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

plus

any two of the following risk factors:

- Family history of type 2 diabetes in first or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or PCOS)
- Maternal history of diabetes or GDM

Age of initiation: age 10 years or at onset of puberty, if puberty occurs at a younger age
Frequency: every 2 years
Test: FPG preferred

CLASSIFICATION OF GLYCEMIA DISTURBANCES

CATEGORIES (STAGES)

- normoglycemia

- hyperglycemia :

1. Impaired regulation of glucose metabolism:
a) Impaired glucose tolerance – **IGT**
b) Impaired fasting glycemia – **IFG**

2. Diabetes mellitus:
a) does not require insulin,
b) requires insulin to well metabolic control,
c) requires insulin to survival.

ETHIOLOGICAL TYPES (PROCESSES)

TYPE 1
- Autoimmunologic,
- Idiopathic.

TYPE 2
Combination of insulin resistance and insulin secretory defect.

OTHER SPECIFIC TYPES
- Genetic defects of beta-cells function
- Genetic defects in insulin action
- Diseases of the exocrine pancreas
- Endocrinopathies (i.e. acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism)
- Diabetes induced by drugs and other chemical substances, i.e. :
  - Vacor
  - Pentamidine
  - Nicotinic acid
  - Glucocorticosteroids
  - Thyroid hormones
  - Diazoxide
  - α-mimetics
  - β-adrenolitics
  - Thiazids
  - Dilantin
  - α-Interferon
- Diabetes induced by viral infections
- Uncommon forms of immune mediated diabetes
- Genetic syndromes sometimes associated with diabetes

GESTATIONAL DIABETES MELLITUS
Diabetes that begins in pregnancy

THE METABOLIC SYNDROME

(European guidelines on cardiovascular disease prevention in clinical practice 2003, National Cholesterol Education Program in the USA, ATPIII 2003)

We diagnose the metabolic syndrome if at least 3 of the following components are present

1. Central (abdominal) obesity:

   perimeter of waist > 102 cm in man
   perimeter of waist > 88 cm in women

   WHR for men > 0,90
   for women > 0,85

   and/or BMI > 30 kg/m^2

2. Plasma TAG conc. ≥ 150 mg/dl
3. Plasma HDL-CH conc. < 40 mg/dl (1,0 mmol/l) in men , < 50 mg/dl (1,3 mmol/l) in women
4. Blood pressure ≥ 130/85 mmHg
5. Fasting plasma glucose concentration ≥ 100 mg/dL (5,6 mmol/l)

WORLDWIDE DEFINITION OF THE METABOLIC SYNDROME

The IDF (International Diabetes Federation) consensus – April 2005

To be defined as having the metabolic syndrome one must have

CENTRAL OBESITY

waist circumference for Europid men ≥ 94 cm and Europid women ≥ 80 cm
(with ethnicity specific values for other groups)

plus any two of the following four factors:

1. raised TAG concentration ≥ 1,7 mmol/l (150 mg/dl)
   or treatment for hypertriglyceridemia
2. reduced HDL- cholesterol conc.:
   males < 1,03 mmol/l (40 mg/dl)
   females < 1,29 mmol/l (50 mg/dl)
   or treatment for this lipid abnormality
3. raised blood pressure:
   systolic ≥ 130 mmHg
   or diastolic ≥ 85 mmHg
   or antyhypertensive treatment
4. raised fasting plasma glucose (FPG) conc. ≥ 5,6 mmol/l (100 mg/dl)
   or previously diagnosed t.2 DM

if FPG ≥ 5,6 mmol/l (100 mg/dl),
OGTT is strongly recommended but is not necessary to define the syndrome

WORLDWIDE DEFINITION OF THE METABOLIC SYNDROME

- different criteria for central obesity in the world. IDF, 2005

Country/Ethnic group	Waist circumference	
Europids	male	≥ 94 cm
	female	≥ 80 cm
in the USA, the ATP III values are likely to continue to be used for clinical purpose	male	≥ 102 cm
	female	≥ 88 cm
South Asians based on a Chinese, Malay and Asian-Indian population	male	≥ 90 cm
	female	≥ 80 cm
Chinese	male	≥ 90 cm
	female	≥ 80 cm
Japanese	male	≥ 85 cm
	female	≥ 90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available.	
Sub-Saharan Africans	Use European data until more specific data are available.	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available.	

TESTING OF BLOOD GLUCOSE CONCENTRATION

- in general

1. The presence of classic diabetic symptoms – the diagnosis of diabetes.
2. The screening for diabetes – in the high risk groups.
3. The testing for carbohydrate metabolism in some specific situations :
    - chronic liver diseases
    - acute liver disease
    - acute pancreatitis
    - chronic pancreatopathy
    - acromegaly
    - Cushing syndrome
    - steroid therapy

THE MONITORING OF DIABETES MELLITUS – LABORATORY TESTS

LABORATORY TESTS FOR CHRONIC MONITORING

testing the threat of late diabetic complications:

- blood glucose levels and self-monitoring of blood glucose (SMBG):
  fasting plasma glucose concentration (FPG),
  postprandial (PPG) 1-2 h after the beginning of the meal,
  profile of diurnal glycemia:

FULL	SHORTENED
fasting in the morning	fasting in the morning
before each main meal	
2 h after each main meal	2 h after each main meal
before sleeping	
at 24:00	
at 3:30	

- markers of backdating glycemia:
  (glucosuria): 2-3 hours
  glycated serum proteins, mainly albumin (fructosamine): 2-3 weeks
  glycated hemoglobin (HbA_{1C}): 2-3 months
- fasting lipid profile in blood: LDL-C, TG, HDL-C
- liver function tests (with further evaluation for fatty liver or hepatitis if abnormal)
- test for microalbuminuria
- renal function tests: creatinine in blood
- *thyroid-stimulating hormone (TSH) in type 1 DM, in type 2 if clinically indicated*
- routine urinalysis

LAB TESTS	FREQUENCY OF ORDERING	COMMENTS
blood glucose	depended on particular needs and goals	patients on insulin need SMBG more frequently than those not using insulin
HbA_{1C} in blood	at least two times a year	Fig.16
fructosamine	not established	• expecting results after adding to or modifying treatment, • if factors disturbing GHB measurements are present (Fig.16)
lipids in blood	at least annually	more often if needed to achieve goals
urinalysis	annually	
microalbuminuria	annually	
creatinine in blood	annually	

THE RELATIONSHIP BETWEEN HbA_{1C} AND MEAN PLASMA GLUCOSE CONCENTRATION

according to the methods of HbA_{1C} measurement certified in the National Glycohemoglobin Standardization Program NGSP, 2006 (www.ngsp.org)

HbA_{1C} (%)	approximate mean plasma glucose concentration	
	mmol/L	mg/dL
4	3,5	65
5	5,5	100
6	7,5	135
7	9,4	170
8	11,4	205
9	13,3	240
10	15,3	275
11	17,2	310
12	19,2	345

Mean plasma glucose concentration – on multiple testing (glucose profiles) over 2-3 months. *Diabetes Care* 25:275-278,2002

FACTORS THAT INTERFERE WITH HbA_{1C} TEST RESULTS

updated 06/2006, www.ngsp.org

1. Hemoglobin Variants and Derivatives:
   - genetic variants (e.g. HbS trait, HbC trait) and
   - chemically modified derivatives of hemoglobin, i.e.:
     carbamylated Hb in patients with renal failure,
     acetylated Hb in patients taking large amounts of aspirin.

2. Shortened Erythrocyte Survival.
   Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (i.e. recovery from acute blood loss, hemolytic anemia) will falsely lower GHB test results regardless of the assay method used .

3. Other factors:
   - Vitamins C and E are reported to falsely lower test results, possibly by inhibiting glycation of hemoglobin; vitamin C may elevate values with some assays as well.
   - Iron-deficiency anemia is reported to increase test results.
   - Hypertriglyceridemia,
     Hyperbilirubinemia,
     Uremia (see carbamylated Hb),
     Chronic alcoholism,
     Chronic ingestion of salicylates,
     Opiate addiction

     } are reported to interfere with some assay methods, falsely increasing results

CRITERIA FOR WELL-CONTROLLED DIABETES
- monitoring of glycemia

CRITICALLY ILL PATIENTS	
plasma glucose level	**close to 110 mg/dl** *6,1 mmol/l* generally < 180 mg/dl *10,0 mmol/l*
NON-CRITICALLY ILL PATIENTS	
blood glucose levels • fasting / preprandial	**90 - 130 mg/dL** *5,0 – 7,2 mmol/L* (midpoint of range 110 mg/dl)
• postprandial	**< 180mg/dL** *< 10,0 mmol/L*
Hb A_{1C} [%Hb}	**< 7.0 %**
	≤ 6,1 to **≤ 6,5 %**

Key concepts in setting glycemic goals:

1. Goals should be individualized.
2. Certain populations (children, pregnant women, and elderly) require special considerations.
3. Less intensive glycemic control may be indicated in patients with tendency to severe (or frequent) hypoglycemia.
4. More stringent glycemic goals (i.e. a normal HbA_{1C} < 6 %) may further reduce complications at the cost of hypoglycemia (in type 1 DM especially)

CRITERIA FOR WELL-CONTROLLED DIABETES
- monitoring of serum lipid concentrations

plasma **T-C** * mg/dl (*mmol/l*)	**< 175** ***(4,5)***	* not recommended by ADA 2006
plasma **LDL-C** mg/dl (*mmol/l*)	**< 100** ***(2,5)***	
plasma **LDL-C** ** mg/dl (*mmol/l*)	**< 70** *(1,9)*	** if DM + CHD
plasma **HDL-C** mg/dl (*mmol/l*)	Male: **> 40** *(1,0)* Female: **> 50** ***(1,28)***	
non-HDL – C mg/dl (*mmol/l*)	**< 130** *(3,4)*	
plasma **TAG** mg/dl (*mmol/l*)	**< 150** ***(1,7)***	

TESTING FOR MICROALBUMINURIA

- in type 1 diabetic patients who have had diabetes for at least 5 years; in some case of pubertal children before 5 years of the disease,
- all patients with type 2 DM.

Screening for microalbuminuria can be performed by three methods:

1. Measurement of the albumin-to-creatinine ratio in a random urine specimen - preferred.
2. 24-h collection.
3. Timed (i.e. 4-h or overnight) collection.

Two of three specimens collected within a 3- to 6-months period should be abnormal.

CATEGORY	**spot collection** **mg/ 1g of creatinie**	**24-h collection** mg/ 24 hrs
normal	**< 30**	< 30
microalbuminuria	**30-299**	30-299
macroalbuminuria	**≥ 300**	≥ 300

The following factors may elevate urinary albumin excretion:

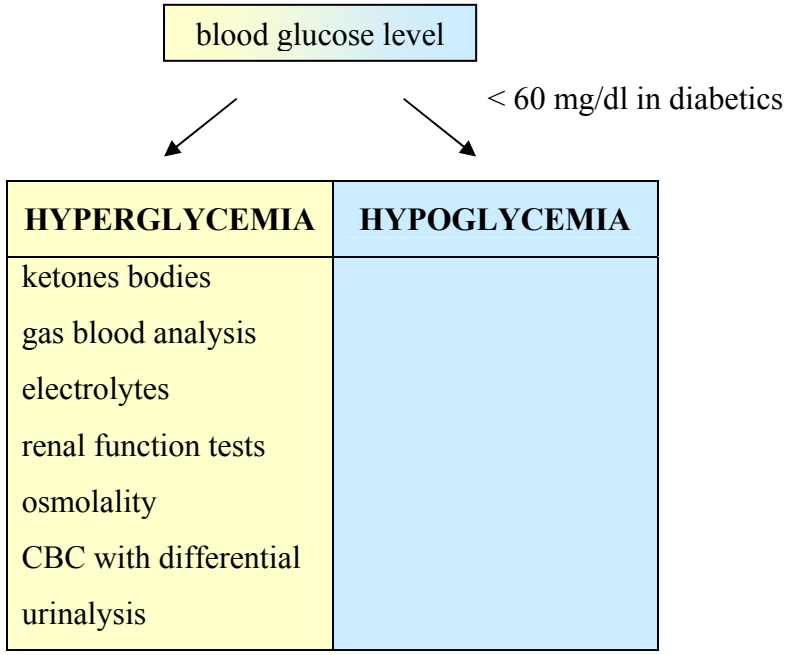
1. exercise within 24 hrs
2. infection
3. fever
4. congestive heart failure
5. marked hyperglycemia
6. marked hypertension.

LABORATORY FINDINGS IN ACUTE SITUATIONS IN DIABETES

Differential diagnosis of falling-in-coma diabetics because of glycemia disturbances:

ADA, Diabetes Care 27:suppl.1,2004

Figure 22.

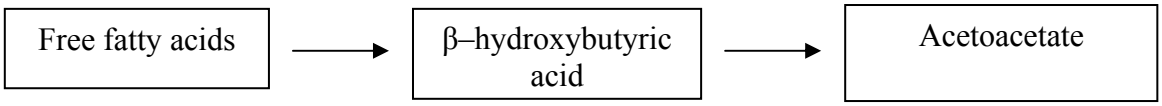


THE EVALUATION OF KETONE BODIES

1. Special meaning in the monitoring of:
- type 1 DM
- diabetic pregnant woman
- gestational diabetes
- acute diseases that can affect diabetes (i.e. severe inflammation enhances requirement for insulin)

2. In other situations make the decision of assessment, if:
- consistent hyperglycemia > 300 mg/dl (16,7 mmol/l) ,
- clinical symptoms of ketoacidosis

3. Patobiochemistry:



4. Measurement: determined in blood — determined in urine by test strips

DIAGNOSTIC CRITERIA FOR

DIABETIC KETOACIDOSIS (D K A)				HYPERGLYCEMIC HYPERMOLAR STATE (H H S)
MILD	MODERATE	SEVERE		
>250(14) [>350(19,4]	>250 [>350]	>250 [>500(27,8)]	**GLUCOSE** mg/dL(mmol/L)	>600
7,25-7,35	7,00-7,24	<7,00	**pH**	>7,30
15-18	10-15	<10	**HCO_3^-** mmol/L	>15
+	+	+	**KETONURIA**	–/+
	c a n v a r y		**OSMOLALITY** mOsm/kg	>320
>10	>12	>12	**ANION GAP** mmol/L	<12
none	none or weakness/ sleepiness	sleepiness/ faintness/ stupor/coma	**DISTURBANCES OF CONSCIOUSNESS**	faintness/ stupor/ coma

CAUSES OF HYPOGLYCEMIA

FASTING HYPOGLYCEMIA

I. Underproduction of glucose.

A. Hormone deficiencies
1. Hypopituitarism
2. Adrenal insufficiency
3. Glucagon insufficiency

B. Enzyme defects
1. Glucose 6-phosphatase
2. Liver phosphorylase
3. Pyruvate carboxylase

C. Substrate deficiency
1. Ketotic hypoglycemia of infancy
2. Severe malnutrition
3. Late pregnancy

D. Acquired liver disease
1. Hepatic congestion
2. Severe hepatitis
3. Cirrhosis
4. Uremia

E. Drugs
1. Alcohol
2. Salicylates.

II. Overutilization of glucose

A. Hyperinsulinism
1. Insulinoma
2. Exogenous insulin
3. Autoimmune disease with antibodies
4. Endotoxic shock

B. Appropriate insulin levels
1. Extrapancreatic tumors
2. Cachexia with fat depletion.

REACTIVE (POSTPRANDIAL) HYPOGLYCEMIA

I. Alimentary hyperinsulinism
II. Hereditary fructose intolerance
III. Galactosemia
IV. Leucine sensitivity
V. Idiopathic.

LABORATORY DIAGNOSIS OF HYPOGLYCEMIA

1. PLASMA GLUCOSE CONC. < 45mg/dL (2,5 mmol/L)

2. IRI/G ratio $\frac{\text{Insulin (μU/L)}}{\text{glucose (mg/dL)}}$ < 0,3 (0,4)

3. PLASMA C-PEPTIDE MEASUREMENT
1,0 –2,0 μg/L (0,33-0,55 nmol/L

4. PROLONGED FASTING
- during 24-72 hour fast – only liquids,
- blood glucose and insulin levels at least every 12 hours and at any time of hypoglycemic symptoms

5. OGTT
- the 5-hour OGTT,
- blood glucose and insulin concentrations.

6. SUPPRESSION OF ENDOGENOUS INSULIN
- 0,1 U/kg body weight insulin i.v. infusion
- within 60 min. plasma glucose conc. decreases to about 45 mg/dL and plasma C-peptide conc. < 1,2 μg/L

7. GLUCAGON PROVOCATIVE TEST
- 1 mg i.v.
- quick raise of glycemia and return to baseline within 90 minutes.

Age-dependent characteristics of laboratory tests

Sylwia Dzięgielewska MD

Biochemical and physiological age-related changes and the consequences

Organ/System	Biochemical/Physiological Change	Consequence of Aging not Disease	Consequence of Disease not Aging
General	↑ body fat	Cholesterol/triglicerydes/ glucose ↑ progressively	obesity, metabolic syndrome
Respiratory	↓ Lung elasticity and ↑ chest wall stiffness	↓ **pO_2** approximately 5% every 15yr. after 30 ↑ **pCO_2** approximately 2% every 10 yr. after 50	dyspnea, hypoxia, hypercapnia
Gastrointestinal	↓ hepatic function	↓ albumin 10-15% after 30 ↓ ALT, AST ↑ Clotting factors VII & VIII	cirrhosis
	↓ gastric acidity	↓ Ca^{2+}	osteoporosis, B12 deficiency
Renal	↓ GFR	↓ creatinine clearance 0,8 ml/min/1yr after 40	↑ serum creatinine
Genitourinary	Prostate enlargement	↑ PSA	prostate cancer
Hematologic	↓ bone marrow reserve	↓ Hb, ↓Ht, ↓RBC	anemia
	↓ T cell function	↓ WBC	
	↑ Autoantibodies	↑ IgA, ↓ IgG & IgM, false-positive RF	autoimmune diseases
Endocrine	Impaired Glucose Homeostasis	**fasting glucose** ↑ 1-2 mg/dl/10 yr. after 40 **postprandial glucose** ↑ 4 mg/dl/10 yr. after 40	diabetes mellitus
	↓ thyroid hormone clearance and production	↓ T3 concentration	thyroid dysfunction
	↑ ADH, ↓ rennin, ↓ aldosterone	↑ ADH, ↓ rennin, ↓ aldosterone	↓ Na^+, ↑ K^+
	↓ Testosterone	↓ Testosterone	impotence
	↓ calciferol absorption and activation	↓ 1,25 $(OH)_2$ vit D	osteoporosis, fractures
Musculosceletal	↓ Bone density	↑ Alkaline phosphatase	

Diseases screening according to age

- Age-dependent diseases: definitely occurring with age

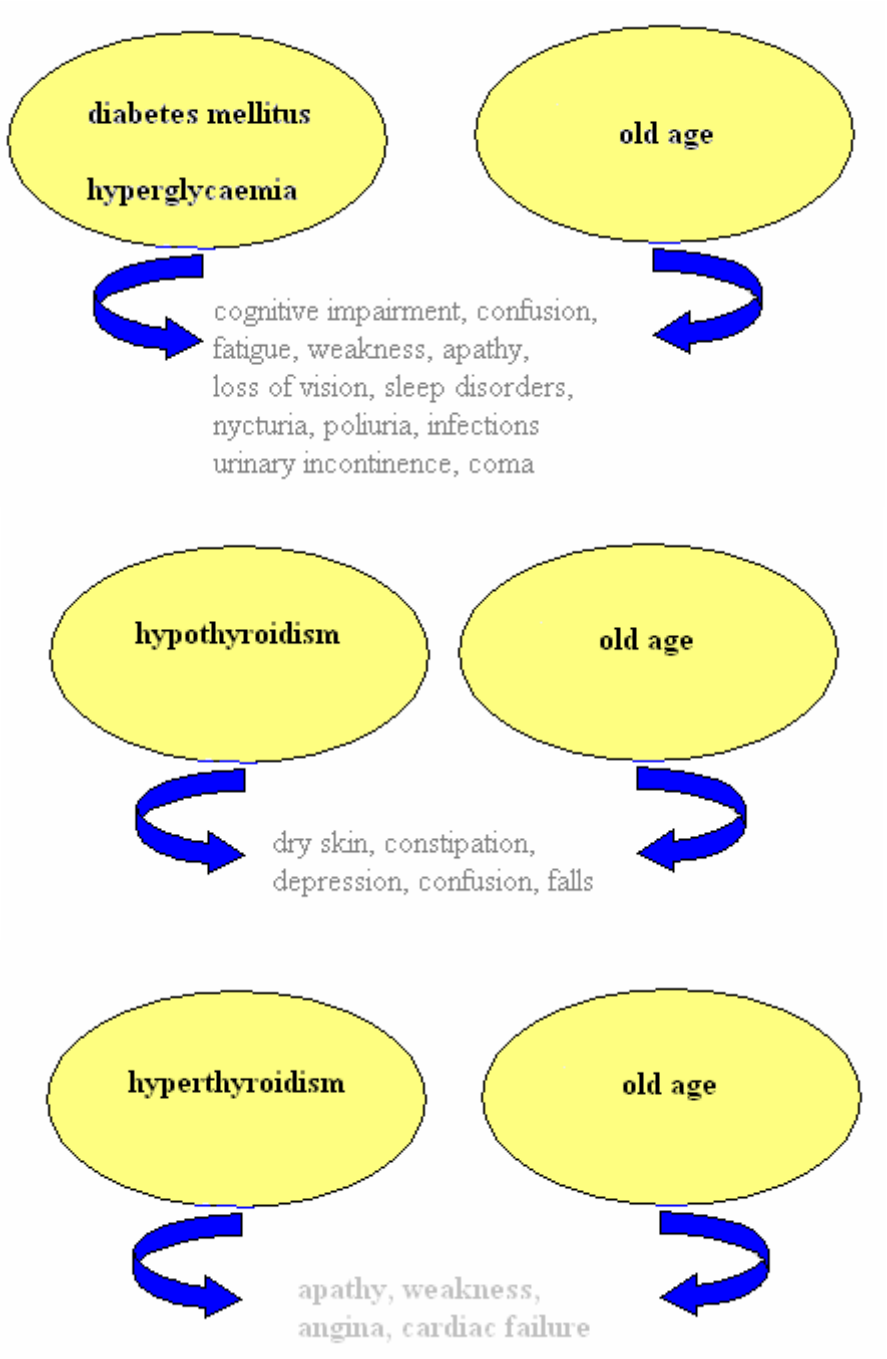
  eg. cataracts, vulvovaginal atrophy (women), nodular prostate hyperplasia (men), brain cell loss, weak immune system (monoclonal gammopathy)

- Age-related diseases: increasing in prevalence with age

  eg. arteriosclerosis (stroke, heart attack, etc.), myelodysplastic syndrome, plasma cell myeloma, hypertension, type II diabetes, Alzheimer's disease, idiopathic Parkinson's disease, cancer: skin, breast, prostate, colon, "atrophic gastritis" (stomach cancer precursor), chronic renal failure, heart failure, Paget's disease of bone, glaucoma, iatrogenic disease and polypharmacy ("vulnerability to infections")

Disease	Recommendations	Comments	Organization
diabetes mellitus	**Fasting glucose** at 3 years interval, men & women >= 45 yr., earlier and more often in patient with risk factors	Risk factors: 1. obesity >25 kg/m^2 2. family history of DM 3. membership of ethnic groups 4. IGT/IFG 5. GDM or mother with infant birth weight >9 Ib or 4,5 kg 6. HA >140/90 mmHg 7. HDL < 35mg/l (0,9 mmol/l) or TG ≥ 200 mg/dl (2,2mmol/l) 8. PCO 9. history of CVD	ADA (2004)
cholesterol & lipid disorders	**Total cholesterol** and **HDL-cholesterol** periodicity based on risk factors men >= 35 yr. women >=45 yr.	1. Age to stop screening is not established. 2. Optimal interval for screening is uncertain.	AAFP (2002) USPSTF (2001)
	Fasting lipoprotein panel every 5 years men and women > 20 yr.	NCEP III promote more aggressive primary prevention in persons with multiple risk factors for CHD	NCEP III (2002)
thyroid disease	Screen with **serum TSH** Women >= 35 yr.	At 35 age and every 5 years thereafter	ATA (2000)
	Women >=50 yr.	Selective screening for patient with 1 or more general symptoms as fatigue, weight gain, depression	ACP (1998)
	Elderly	Periodic screening with sensitive TSH	AACE (2002)
chronic kidney disease	Every patient >65 yr. Cystatine C or GFR **GFR 60-89 mL/min/1,73 m^2 or less evaluate GFR every 3 months**	1. Evaluate CVD risk 2. measure BP 3. albumin and creatinine concentration in urine 4. RBC and WBC in urine	NKF (2003)

Clinical manifestation of diseases in elderly may be misinterpreted as normal aging



to differentiate:
past history → physical examination → lab tests:

1. **CBC,**
2. **glucose concentration,**
3. **electrolytes,**
4. **TSH, fT4, fT3,**
5. **ALT, AST, GGTP,**
6. **urine examination.**

Disease	Recommendations	Comments	Organization
heart failure	If suspected because of symptoms/signs – 1. ECG 2. X-Ray 3. **BNP**	BNP if available to identify patients with elevated left ventricular filling pressures, **marker of morbidity and mortality** in patients with known HF and as an aid in differentiating dyspnea due to HF from dyspnea due in other cases. Risk factors: 1. CHD 2. SBP >= 140 mmHg 3. CRP > 7 mg/l 4. DM 5. creatinine >1,4 mg/dL	ESC HF (2001)
prostate cancer	Asymptomatic men	Insufficient evidence to recommend for or against routine screening by PSA	NCI (2004) AAFP (2004)
colorectal cancer	Aged >=50 yr.	FOBT annually + flexible sigmoidoscopy every 5 years or colonoscopy or barium enema	AAFP (2004)

Age-dependent reference range for PSA

age	PSA (ug/L)
40-49	0,0-2,5
50-59	0,0-3,5
60-69	0,0-4,5
70-79	0,0-6,5

Monitoring diseases in old patients

Disease	Recommendations	Comments	Organization
Diabetes Mellitus	1. glycemic control 2. lipids profile 3. micro- / macroalbuminuria 4. BP control < 130/80 mmHg 5. body weigh control 6. physical activity	1. Target hemoglobin A_{1c} should be individualized. 2. A reasonable goal for **Hb A_{1c} is 7%** or lower for relatively healthy elderly. 3. For frail older adults with **life expectancy of less than 5 years** and others in whom the risk of intensive glycemic control appear to outweigh the benefits appropriate **Hb A_{1c} is 8%** 4. Elders should have his/her **Hb A_{1c}** measured **at least every 6 months if** individual **target is not being met**. 5. For persons with **stable Hb A_{1c}** over several years measurement every **12 months** may be appropriate. 6. The goal is **100 mg/dL or less** in old adult with DM, when elderly patient with DM has an LDL cholesterol concentration of: 7. After initial screening and in the absence of previously demonstrated macro-microalbuminuria test for the presence of microalbumin should be performed annually.	ADA (2003/2004)

Disease	Recommendations	Comments	Organization
Heart Failure	Initial measurment of: 1. CBC 2. urinalysis 3. serum electrolytes (including Ca^{2+}, Mg^{2+}) 4. BUN 5. serum creatinine and creatinine clearance 6. fasting glucose 7. lipids profile 8. liver function tests 9. TSH	1. Measurements for identifications of the disorder leading to HF – some of them are reversible or treatable. 2. If ACE inhibitors, aldosterone inhibitors – renal function and Na^+, K^+ at start and after 2 weeks (avoid hyperkalemia). 3. If diuretics (loop, thiazides), digitalis – measure K^+ at frequent intervals to avoid hypokalemia	ACC/AHA (2003)
Coronary Heart Disease	1. lipids profile 2. glycemic control 3. electrolytes 4. BP control < 140/90 mmHg 5. body weigh control 6. physical activity	1. Age to stop monitoring is not established, the goals: LDL cholesterol <100 mg/dL (<70 mg/dL), HDL cholesterol : men > 45 mg/dL, women > 50 mg/dL, TG < 180 mg/dL *diabetics TG < 150 mg/dL* **If LDL:** **100 mg/dL or less** – check lipid status **at least every 2 years**, **100-129 mg/dL** - check lipid status **at least annually,** MNT, increased physical activity **130 mg/dL or grater** - check lipid status **at least annually**, pharmacological therapy to achieve the goal NCEP III promote more aggressive primary prevention in persons with multiple risk factors for CHD 2. when treatment control at frequent intervals electrolytes	AAFP (2002) USPSTF (2001) NCEP III (2002)
Renal failure	1. electrolytes (Na^+,K^+,Cl^-,HCO_3^-,Ca^{2+}) 2. CBC 3. serum albumin 4. PTH 5. BUN 6. lipids profile	To asses other clinical conditions common in renal failure	NKF (2003)

1. Measured creatinine clearance

$$cc\ (mL/min) = [U \times V] / P$$

U- urine concentration of the creatinine (mg/dl)
P- plasma concentration of the creatinine (mg/dl)
V- urine flow rate (ml/min)

2. Estimated creatinine clearance according to the Cockcroft-Gault formula

$$cc\ (mL/min) = [(140 - age\ (years)) \times body\ mass\ (kg)] / [72 \times serum\ creatinine\ (mg/dL)]$$

for women multiply by 0,85

Palliative care for elderly people

According AAHPM 2004

Who is terminally ill?

Usually anyone who is 65 or older; or on hemodialysis and the patient's medical prognosis is 6 months or less, if the disease runs its normal course – 2 Physicians **MUST SIGN a statement about patient's medical prognosis**

How to determine prognosis of 6 month or less?

- **Heart disease** – recurrent heart failure or angina at rest – NYHA Class IV, patient already optimally treatment with diuretics and vasodilators, EF <=20%.

- **Pulmonary disease** - progressive pulmonary disease/respiratory failure, disabling dyspnea at rest

  1. Hypoxemia at rest on supplemental O_2:
  - pO2 =< 55 mmHg on supplemental O_2
  - S O_2 =< 88% on supplemental O_2 **or**

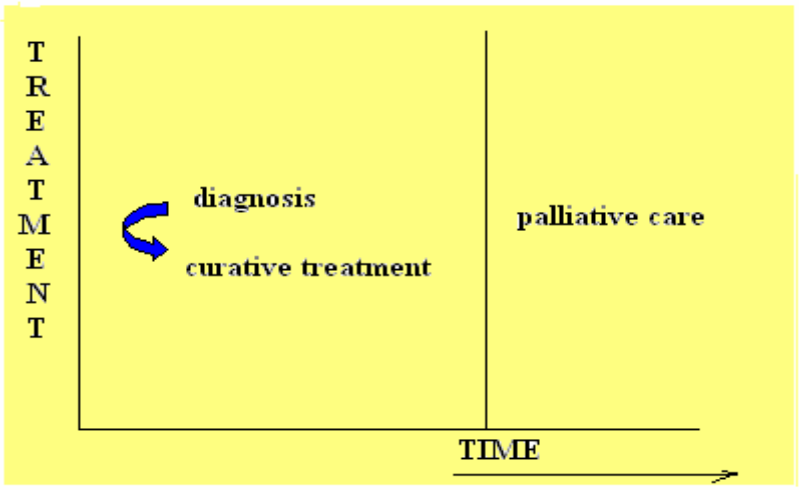
  2. Hypercapnia
  - pCO_2 >= 50 mmHg

- **Liver disease** – end-stage cirrhosis – not candidate for liver transplant
  - PT > 5 sec or INR >1,5 and serum albumin <2,5 g/dl

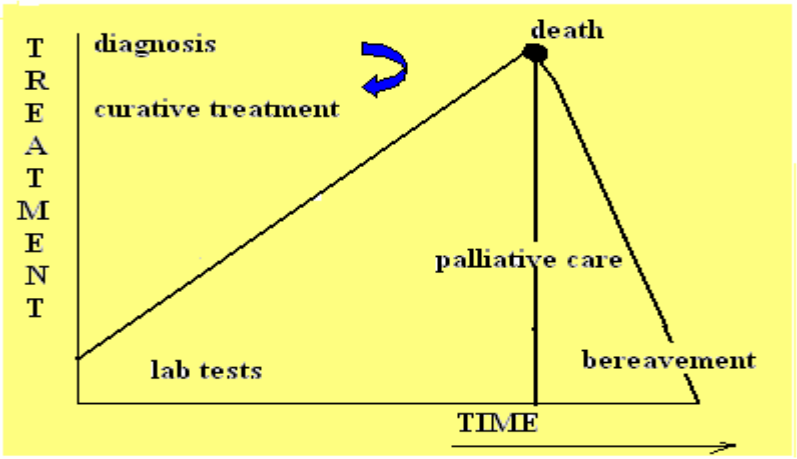
  At least one of : ascites despite diuretics and low sodium diet
  spontaneous peritonitis
  hepatorenal syndrome
  hepatic encephalopathy
  recurrent variceal bleed

- **Renal disease** – chronic renal failure, not a candidate for dialysis
  - creatinine clearance < 10 cc/min (for DM < 15 cc/min)
  - serum creatinine > 8,0 mg/dl (for DM > 6,0 mg/dl)
  - hyperkalemia – serum K^+ > 7,0 mmol/l

1. Traditional concept of diagnosis, treatment and palliative care



2. New concept of palliative care



ABREVIATIONS

ACE	angiotensin-converting enzyme
ADH	antydiuretic hormone
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotranferase
BNP	brain natriuretic peptide
CBC	complete blood count
CHD	coronary heart disease
CHF	congestive heart failure
CVD	cardiovascular disease
DM	diabetes mellitus
ECG	electrocardiography
FOBT	fecal occult blood test
GDM	gestational diabetes mellitus
HA	hypertonia aterialis
HDL	high-density lipoprotein
HF	heart failure
Hb	hemoglobin
Ht	hematocrit
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
LDL	low-density lipoprotein
NSAIDs	non-steroids anti-inflammatory drugs
PCO	polycystic ovary
PSA	prostate-specific antigen
RBC	Red Blood Cell
RF	rheumatic fever
SBP	Systolic Blood Pressure
TG	triglicerydes
TSH	thyroid stimulating hormone
WBC	White Blood Cell

AACE	American Association of Clinical Endocrinologists
AAFP	American Academy of Family Physicians
ACP	American College of Physicians
ADA	American Diabetes Association
AHA	American Heart Association
ATA	American Thyroid Association
ESC	European Society of Cardiology
USPSTF	United States Preventive Services Task Force
NCEP III	National Cholesterol Education Program
NCI	National Cancer Institute
NKF	National Kidney Fundation

REFERENCES

1. Braunwald E., Fauci A.S., Isselbacher K.J., Kasper D.J., Hauser S. L., Longo D. L., and Jameson J.L., „Harrison's Principles of Internal Medicine" Part 1, Chapter 8: Geriatric Medicine, 16th ed. Mc Graw-Hill 2004-2005,
2. Beers M.H., Berkow R., „Merck Manual of Geriatrics" App. I Laboratory Values. Merck and Co, Inc., Internet Edition May 2005,
3. California Healthcare Foundation/American Geriatrics Society (AGS) Panel on Improving Care of Elders with Diabetes and approved by the AGS Board of Directors on February 25, 2003, "Guidelines for Improving the Care of the Older Person with with Diabetes Mellitus", JAGS 2003, 51:S265-S280,
4. "Heart Disease and Stroke Statistics — 2005 Update", American Heart Association
5. Brigden M. L., Heathcote J. C., "Problems in interpreting laboratory tests, What do unexpected results man?" Postgrad. Med. 2000, Jun, Vol 107, No 7,
6. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G, "National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification", Ann Intern Med. 2003 Jul 15;139(2):137-47,
7. Finney H., Bates C.J., Price C.P., "Plasma cystatin C determinations in healthy elderly population", Arch. Gerontol. Geriatr. 29: 75-94, 1999,
8. Fliser D., Ritz E., „Serum cystatin C concentrations as a marker of renal dysfunction in elderly", Am. J. Kidney Dis. 2001, 1: 79-83,
9. Morgan T.O., Jacobsen S.J., Mc Carthy W.F., "Age specific reference ranges for serum prostate-specific antigen." N. Engl. J. Med. 1996;335;304-310,
10. Lynn J. Adamson DM. „Living well at the end of life: adapting health care to serious chronic illness in old age." Arlington, VA, Rand Health 2003,
11. E. Davies and I.J. Higginson "Better Palliative Care for Older People" WHO on line recommendations 2003,
12. Fenigsen R., "The report of the Dutch Governmental Committee on Euthanasia" Issues Law Med. 1991 Winter;7(3):339-44.