Nephrology and hypertension lecture notes for medical students

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PÉCSI TUDOMÁNYEGYETEM
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Chapter 1.
Introduction
Dr. István Wittmann

Introduction

In the words of our teachers: "All large discoveries begin with a case report" (according to János Radó), and "The deceased teach the living" (from the legendary György Romhányi).

It was also our teacher, György Romhányi, who when talking about the kidney with special enthusiasm called it "organum elegantissimum": the "elegant organ". The figure below depicts this elegance (Figure), showing the wonderful vascular structure of the kidney:

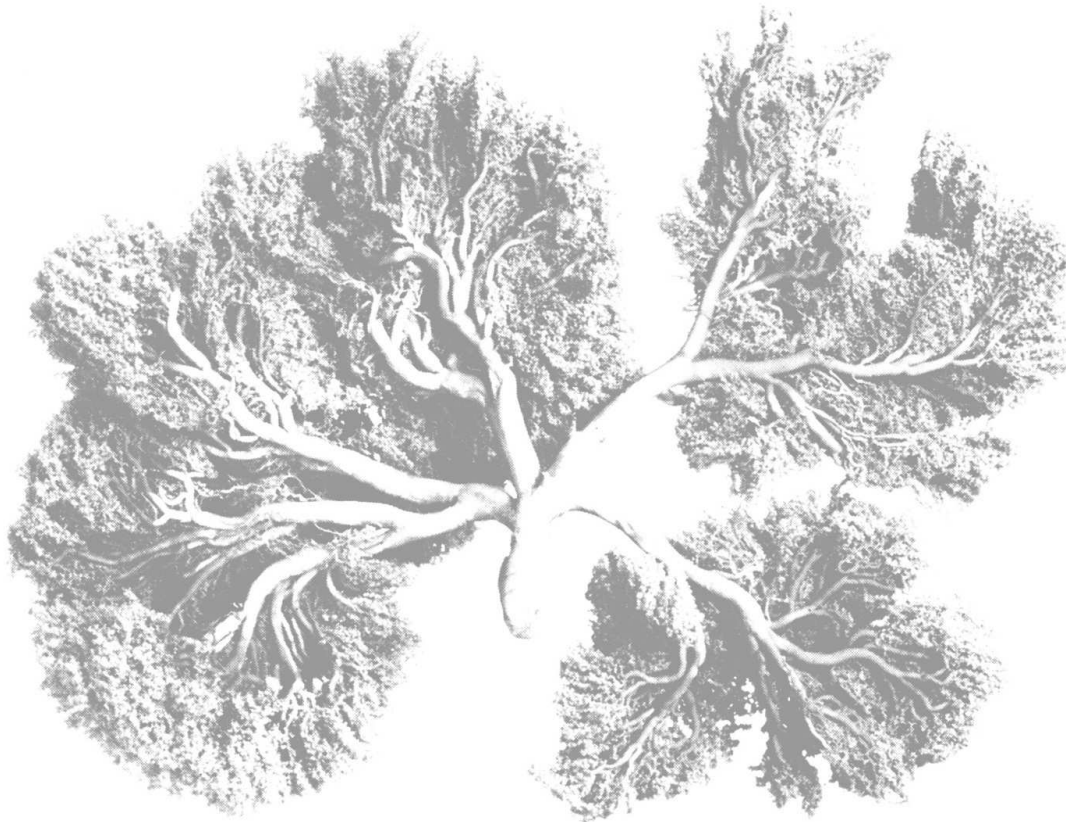**Figure: Vascular system of the kidney**

There is another, general lesson to be learnt from nephrology. It highlights the importance of the diseases of frontier areas; that is, to the scandalous assertion that due to the sub-specialisation of internal medicine we hardly ever consider the sick human being. According to the third important teaching of our tutors, we should never treat the disease, but the patient!

A further complication with nephrology arises from the patient's often being free of complaints and symptoms for a comparatively long time. The characteristics of related problems and their consequences are depicted in Figure.
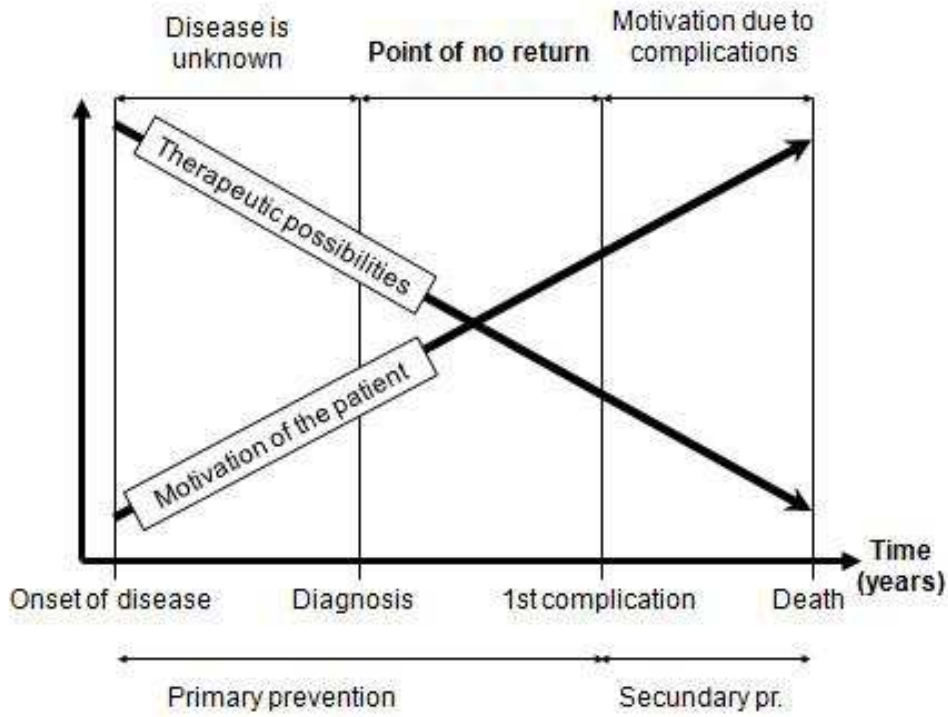
Figure: Renal disease does not cause symptoms or complaints for a long time, and so motivation in the patient is low. At the time of onset of symptoms and complaints, therapeutic possibilities however become limited. Furthermore, primary prevention can in general be carried out in the symptomless phase.

The doctor working in the field of nephrology also has to face another property of kidney diseases, namely that these diseases frequently change their nature due to an explosive improvement of therapeutic options, and also that the acceptance of the knowledge related to them is constantly changing (Figure).
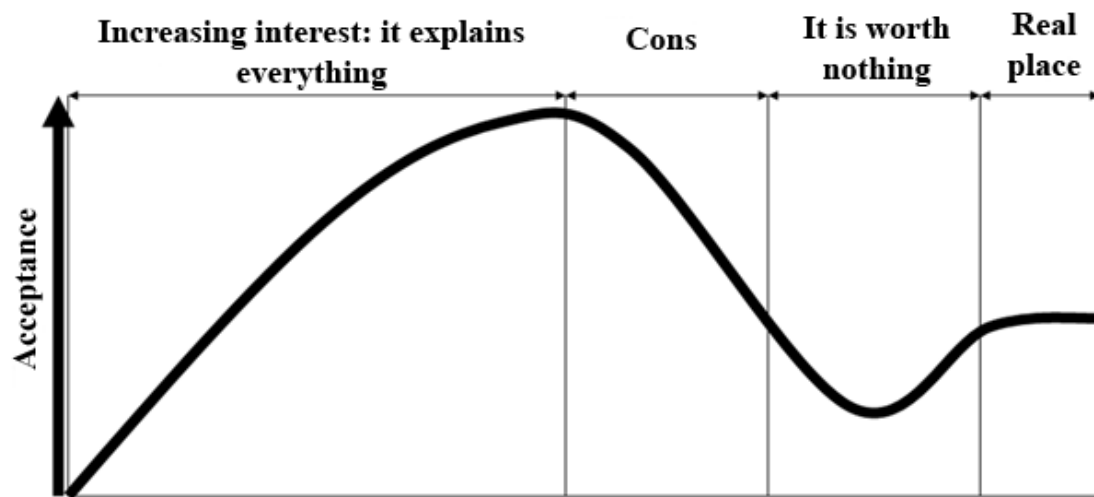
Figure: The nature of clinical knowledge. It can be seen that initially enthusiasm towards new observations is characteristic, along with a huge acceptance. The clinical course of renal diseases may change with increasing therapeutic opportunities, due to which the acceptance of diagnostic and therapeutic approaches may also change.

Chapter 2.
Diagnostic procedures according to major clinical syndromes
Dr. István Wittmann

Case history and physical examination in renal diseases

Case history

Family history is an important factor in the elaboration of **inherited** renal diseases (polycystic kidney disease, Alport syndrome etc.). It is not enough to ask if any relative has undergone renal replacement therapy (dialysis, transplantation); we also have to ask whether any have suffered from high blood pressure or if there was an onset of the disease at young age and/or a blood pressure above 200 mmHg?

When asking the patient about previous diseases, we also have to ask about **high blood pressure** beginning at a young age or above 200 mmHg, or any sudden elevation of blood pressure along with pulmonary oedema (which may be a sign of renal artery stenosis).

Does the patient notice **hematuria?** (The presence of fresh, red blood in the urine may be the sign of coagulopathy, infection, malignancy, lower urinary tract injury or papillary necrosis; while dark-brown urine colour may signify an upper urinary tract bleeding, as the blood turns brown during prolongued periods in the bladder.)

Does the patient notice a change in the **amount of urine** (the decrease may be a sign of renal failure, while an increase may signify diabetes mellitus, insipidus, or compensatory polyuria)?

Change in the diurnal distribution of urine amount: Does the patient have nocturia? CAVE: nocturia is most frequently caused by heart failure, but infection, disease of the prostate, diabetes insipidus, osmotic diuresis due to diabetes mellitus, and compensatory polyuria may also be in the background!

Does the patient show signs of **recurrent urinary tract infections**? Does the patient have unpleasant-smelling (infection) or foamy (proteinuria) urine?

Does the patient have symptoms indicating a **disturbance of urination**: incontinence, difficulties at the start of urination (disease of the prostate)?

Pain: colic pain from the lumbar region radiating towards the pubic area (neprolithiasis, detachment of the papilla). A dull pain in the region of the kidneys (without fever: e.g. acute glomerulonephritis; with fever: pyelonephritis). Lower abdominal pain (diseases of the bladder and lower urinary tract).

Change in body weight: has there been an increase in body weight with concomitant development of oedema (nephritic syndrome, renal failure)? Has there been a decrease in body weight (slowly: chronic renal disease, fast: due to dehydration)?

When suspecting renal disease related to **systemic diseases:** Is there a history of cardiovascular disease, high blood glucose, fever-subfebrility, muscle pain, exanthema, hemoptoe, alcoholic liver disease?

We also have to cover **professional history**. Many poisons are nephrotoxic, some infections may lead to renal damage For instance, leptospirosis, hanta virus infection is more frequent among people working in the forests or fields.

Smoking: Smoking may increase the risk of or speed up the progression of many renal diseases. The amount should be provided always as package-years.

Alcohol and drug abuse: Alcoholics may be more sensitive to certain drugs; a small dose of paracetamol may at the same time lead to hepatic and liver failure (the expression of cytochrome P450 IIE1, the alcoholic isoenzyme may also increase in the kidney). The chance of focal segmental glomerular sclerosis also increases with heroin users.

Pregnancy history: A repeated spontaneous abortion may indicate antiphospholipid syndrome. If the proteinuria persists, a renal biopsy should be carried out. A disease starting with gestational diabetes may go over into a persistent type 1 or type 2 diabetes mellitus, which may lead to renal damage.

Pharmacotherapy and diagnostic tests: Medications in the patient's history may be neprotoxic, while X-ray examination using iodine-containing contrast media may lead to renal damage.

Physical examination
Inspection

Skin symptoms triggered by renal diseases: Here uremic skin should be mentioned firstly, for it is anaemic, grey, dry and shows suffusions.

Systemic or other diseases that have renal and skin manifestations: The renal disease may show all skin lesions of the systemic diseases, where renal affection is also present, such as with rubeosis diabeticorum, vasculitic skin lesions, or icterus in hepatorenal syndrome.

Palpation and tenderness

The kidney may be tender when suffering bacterial inflammation, the acute phase of an autoimmune inflammation and nephrolithiasis. On palpation of the abdomen, we may

reach a ptotic or enlarged kidney, while the ballotation may be painful in a case of inflammation. Tenderness may be noted when the bladder is distended. Anasarca may be palpated in nephrotic syndrome and in renal failure. Lower extremity pulses may be absent in cases of claudication intermittens-related ischemic nephropathy.

Auscultation

A vascular murmur may be heard above the renal arteries in cases of renal artery stenosis.

Diagnosis according to kidney size, imaging tests

One approach in the diagnostics of renal diseases may originate from the size of the kidneys. From this, we can make assumptions not only regarding the disease itself, but also its duration and progressivity. An appropriate step would therefore be for us to ask for an abdominal sonography in the diagnosis of kidney diseases, which should provide numerical data on renal diameters. One should not be satisfied with a diagnosis stating that the "kidneys are normal" based solely on an ultrasonographic description. Table 1 shows clinical syndromes arranged according to size of kidney.

Table: Major clinical syndromes

1. Syndromes of renal enlargement

   a. Syndrome of hyperfiltration

   b. Other syndromes leading to enlarged kidneys

   c. Syndromes with initial, acute kidney enlargement

      i. Bilateral

         1. Acute (glomerulo)nephritic syndrome

         2. Rapid progressive glomerulonephritis syndrome

         3. Syndrome of acute tubulointerstitial nephropathy

         4. Acute kidney injury

      ii. Unilateral

         1. Syndrome of acute urinary tract infection

         2. Renal vein thrombosis (frequently associated with nephrotic syndrome)

2. Syndromes with progressive shrinking of the kidneys

   a. Chronic glomerulonephritis syndrome

b. Nephrotic syndrome

c. Nephroso-nephritic syndrome

d. Chronic tubular nephropathy syndrome

e. Renal artery stenosis (ischaemic nephropathy)

f. Chronic kidney disease syndrome

3. Non-progressive syndromes that cause no alteration in kidney size

a. Oligosymptomatic diseases

Besides kidney size, another important parameter of the ultrasonographic imaging of the kidneys is the surface of the kidneys. Coarse, scarred intrusions may indicate a chronic pyelonephritis, while if there is also a concomitant calcification of the parenchyma and analgesic nephropathy may be present. Fine irregularity of the renal surface may refer to atherosclerosis. The ultrasonography test may verify a solitary kidney, or the malposition or mobility of the kidneys (e.g. ptosis), abnormal structures in the kidney (stone, tumour, cyst), alteration in the echogenity of the parenchyma (e.g. medullary calcification: hyperparathyreosis, sarcoidosis etc., calcification in the cortex: chronic glomerulonephritis). Ultrasonography and Doppler ultrasonography may also detect bleeding or the development of an arterio-venous shunt due to a renal biopsy. Doppler imaging also may help in the detection of renal artery stenosis (a shrunken kidney may be seen on conventional ultrasound) and in the diagnosis of renal vein thrombosis (an acute kidney enlargement may be detected using conventional ultrasound).

Generally, no further imaging is needed to establish the size of the kidneys, but these imaging tests may be required to show additional details. The classical intravenous urography used in the diagnostics of renal diseases has been pushed to the background by computed tomography and MRI. Classical renal angiography is still the most reliable method to diagnose renal artery stenosis. Renal scintigraphy using isotope imaging is today merely and rarely used to diagnose renal embolisation. The same accounts for camerarenography, which today may also be used to diagnose vesico-uretheral reflux.

Syndromes of renal enlargement

Syndrome of hyperfiltration and estimation of glomerular function

Hyperfiltration may be especially typical of the early phase of diabetic nephropathy, but may also occur in other renal diseases (e.g. early phase of renal affection in obesity or

hypertension). It presents itself with an enlargement of the kidneys, a decrease in serum creatinine values below the normal range, or an abnormally high GFR value in an asymptomatic patient.

Today the glomerular function is no longer characterized by serum creatinine measurement, but rather by the serum creatinine-derived estimated GFR (eGFR) or other methods able to measure GFR (i.e. endogenous creatinine clearance or isotope clearance). GFR (eGFR) is estimated today by using the CKD-EPI formula, which is even able to detect hyperfiltration (see also the section on diabetic nephropathy).

Hyperfiltration may be concomitted by a pathologic excretion of albumin in the urine (see later). Similar observations can be made in cases of increased protein or amino acid intake, for instance among body-builders. A special form of the syndrome is represented by a patient with a solitary kidney (from distinct causes), where the remaining kidney shows a compensatory enlargement and hyperfiltration, while the GFR typically shows no increase. Hyperfiltration creates a higher load on the kidneys, and probably increases the chance of progression of renal disease. A schematic drawing demonstrating the connection between hyperfiltration and loss of renal function is shown on Figure.
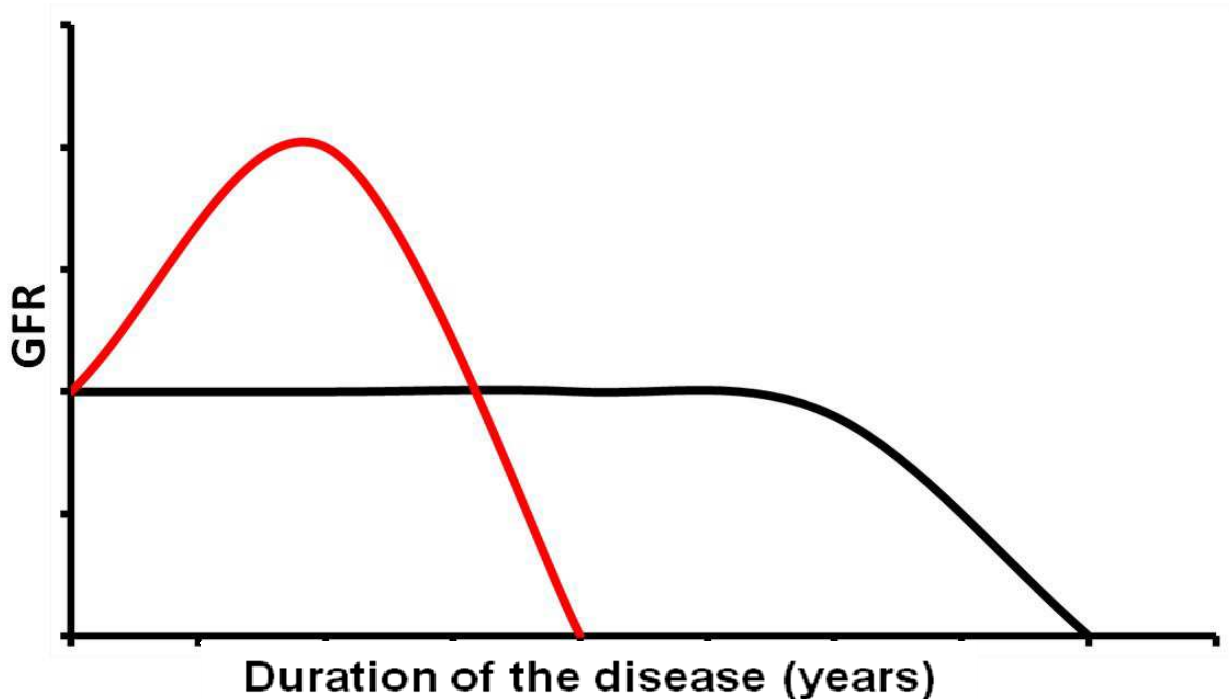
Figure: Schematic representation on the possible role of hyperfiltration (red line) in the development of renal failure.

Others syndromes leading to enlarged kidneys

In cases of amyloidosis, in multiple myeloma bilateral; in cases of renal tumours/malignancies or in cases of hydronephrosis, mainly unilateral; in cystic renal diseases either uni- or bilateral enlargement of the kidneys may be seen. Imaging tests may provide an aid in differentiating between these diseases, but further tests are also required to a further differential diagnosis of amyloidosis and other diseases that come with hyperfiltration.

Syndromes with initial, acute kidney enlargement

A renal enlargement may be seen in many infectious and non-infectious inflammations of the kidney as well as in renal vein thrombosis, where the kidney size may be normalized after healing of the disease.

Acute glomerulonephritis syndrome

A syndrome presenting glomerular-type haematuria (glomHU, Figure), modest (<1g/day) proteinuria (PU), impairment of renal function (GFR$\downarrow$), elevation in blood pressure (RR$\uparrow$), renal enlargement and periorbital oedema (Oe).

Figure: Red blood cells in the urine sediment. Thick white arrows show glomerular-type red blood cells, while black arrows show red blood cells of normal morphology.

Rapid progressive glomerulonephritis syndrome

The symptoms are the same as in cases of acute glomerulonephritis (glomHU, PU, Oe, GFR↓, RR↑) but the decline in GFR is rather fast, and within weeks or months an end-stage renal disease may develop, while the kidneys may be still of normal or large size.
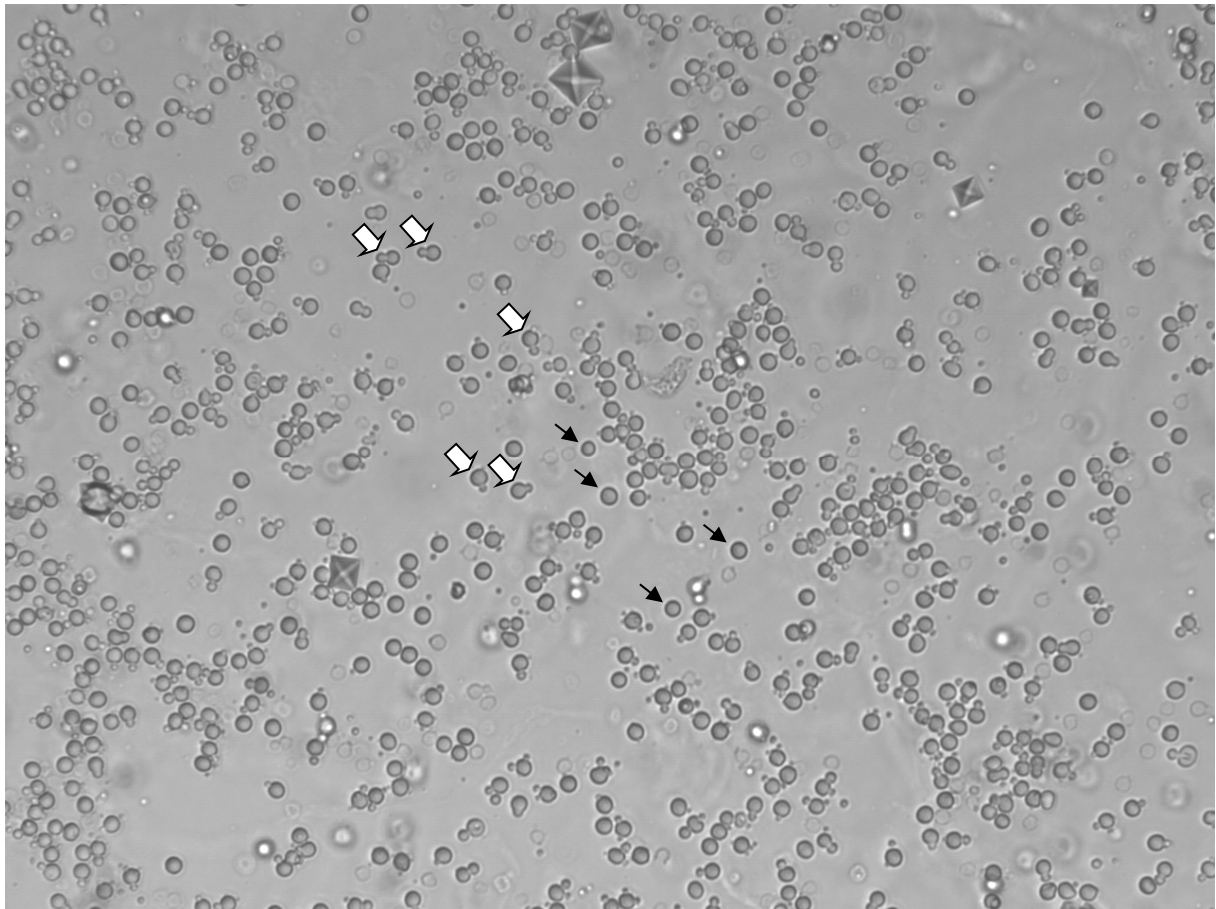
Acute tubulointerstitial nephropathy syndrome

This comprises a group of diseases occurring after exposure to a medication or an infective agent and presenting an inflammatory or hypersensitive reaction, either in a non-oliguric or an oliguric form, showing an elevation in serum creatinine, in some cases eosinophylia, an elevation in IgE, non-glomerular type haematuria, leukocyturia, excretion of epithelial cylinders, non-diabetic glucosuria, aminoaciduria, tubular proteinuria and renal enlargement.

Acute kidney injury

Conditions come along with rapid deterioration (within hours or a day) of kidney function (either of pre- or postrenal or renal origin), frequently associated with failure of other organs and also leading to fluid or electrolyte abnormalities, the postrenal and renal form of which may present itself with the enlargement of the kidney.

Acute urinary tract infection syndrome

Pyelonephritis, but not pyelitis, may be present, with enlargement of the kidney accompanied by fever, chills, flank pain, non-glomerular type haematuria, pyuria, signs of systemic inflammation; and in cases of an ascendant infection, also with dysuria.

Renal vein thrombosis syndrome

Acute renal vein thrombosis is a syndrome of flank pain, nausea, vomiting, leukocytosis, HU, PU – or in the case of an already proteinuric patient with an increase in proteinuria. In cases of a solitary kidney, it may quickly lead to renal failure.

Progressive syndromes with shrinking of the kidneys
Syndrome of chronic glomerulonephritis

A group of diseases mentioned when discussing acute glomerulonephritis (with HU, PU, Oe, GFR↓, RR↑) shows a slow (years- or decades-long) and variable progression, the progressive sub-group of which shows shrinking of the kidneys.

Nephrotic syndrome

Its progressive sub-group may also lead to shrinking of the kidneys, with two exceptions: the rare state of diabetic nephrosis, uncommon today, and the rare onset of amyloidosis: in these two diseases the kidneys may be enlarged for a long time, and subsequent shrinking occurs rather slowly. The major symptoms are nephrotic range (> 3,5 grams/day) PrU, hypopoteinaemia, hypoalbuminaemia, generalized Oe, dyslipidaemia and an increased susceptibility to thrombosis.

Nephroso-nephritis syndrome

This syndrome can be considered in cases where the syndromes of glomerulonephritis and nephrosis present themselves together, i.e. glomHU, PU (> 3,5gr/day), (generalized) Oe, GFR↓, RR↑, hypoproteinaemia, hypoalbuminaemia, dyslipidaemia and susceptibility to thromboses. The progressive subgroup of the syndrome leads to shrinking of the kidneys.

Chronic tubular nephropathy syndrome

Use of analgesics, urinary tract reflux or obstruction may lead to a group of diseases causing non-glomerular HU, leukocyturia, excretion of tubular epithelial cylinders, light tubular PU, glucosuria, aminoaciduria and shrinking of the kidneys.

Renal artery stenosis (ischaemic nephropathy)

This may present itself as different syndromes, in all of which the affected kidney is smaller:

1. Hypertension (secondary, renovascular) with acute kidney injury due to therapy by RAAS-inhibitors.
2. In a patient with known renal artery stenosis, slow decline in renal function (decrease in GFR) develops due to ischemic nephropathy.
3. Resistant hypertension with the decrease of GFR and pulmonary oedema
4. Cases of elderly patients with impaired GFR, and a sudden loss of GFR as a sign of the development of complete obstruction of the renal artery.

Chronic renal insufficiency

This is found in cases of chronic (end-stage) renal insufficiency characterized by shrinking of the kidneys and discoloration of the skin (anaemic, gray), and pruritus; as well as nausea, a decrease in appetite, susceptibility to bleeding, oedema, pleuritis, pericarditis,

hypertension, hypoxia, neurologic signs, susceptibility to infections, decrease in urine output, symptoms of extraosseal calcification, in the laboratory tests an increase in serum creatinine, serum potassium, blood urea nitrogen, serum phosphate and parathormone levels, a decrease in serum calcium and vitamin D, dyslipidaemia, metabolic acidosis and a normocytic normochrom anaemia.

Non-progressive syndromes causing no alteration in kidney size

The non-progressive forms of chronic glomerulonephritis, nephrotic syndrome and nephroso-nephritic syndrome do not lead to a change in kidney size.

Oligosymptomatic diseases

Diseases that lead to glomHU only, or to PU only, or to glomHU+PU, without the presence of other symptoms of a glomerulonephritis or nephrosis, are in general benign, i.e. they do not show progression and do not lead to a shrinking of the kidneys.

Kidney involvement in multiorgan syndromes

In kidney disease the renal symptoms are frequently associated with syndromes or complaints related to involvement of another organ, such as in **kidney-lung** (or pulmo-renal) **syndromes** HU with hemoptoe (in vasculitis or in Goodpasture syndrome), or in **kidney-liver syndromes** liver failure along with renal failure (e.g. hepatorenal syndrome). Behind a **kidney-skin syndrome** or a **kidney-gastrointestinal tract syndrome** or a **kidney-central nervous system syndrome** most frequently systemic autoimmune diseases (e.g. SLE, vasculitis, amyloidosis, hypereosinophylia syndrome, cryoglobulinaemia), or other systemic diseasis (eg. infections, inherited metabolic diseases) may be found. Acute kidney injury may also frequently be a part of an **acute multi-organ failure syndrome**.

The cardio-renal or reno-cardial syndromes are distinct from these; differing both in pathogenesis as well as in importance. There are several possible reasons for its development: most frequently and most importantly for everyday practice as well as for mortality is that risk factors that are at the same time vasculotoxic and nephrotoxic lead to parallel cardiovascular and renal damage, for instance in diabetes mellitus, in hypertension, dyslipidaemia, and obesity. One may also observe cases where a chronic cardiac disease may lead to renal damage (e.g. hypoperfusion of the kidneys due to chronic arrhythmia), or where a renal-originating disease may lead to vascular damage (e.g. chronic glomerulonephritis leading via a decline in GFR and resulting retention of toxic substances).

Clinical syndromes, diagnosis and therapy

      A problem in the diagnosis and therapy of kidney diseases is that determination of the clinical syndrome may not provide the ultimate diagnosis that would be needed for a specific therapy. After determining the clinical syndrome, we have to determine whether a histologic analysis would be required to provide a causal therapy, as this would be the best type of therapy (see in more detail in the chapter on renal biopsy). If no histological analysis is carried out, other methods may be used to find out the cause of the disease and the possibility of a causal therapy. The renal biopsy provides a histologic diagnosis, which may not always show the underlying cause, but based on the histology, we may initiate a search for the cause of the disease. Finally, in a large group of renal diseases no underlying cause may be detected. In these cases we can talk about 'primary' or 'idiopathic' renal disease, and in such cases our knowledge of which 'empiric' therapies may be most useful is based upon earlier studies. A schematic elaboration of kidney diseases based on clinical syndromes is depicted in Figure 6.

Determination of the clinical syndrome

↓

Is a renal biopsy needed?

No → We look for causal diagnosis and therapy → Causal or empiric therapy

Yes → We get a histologic diagnosis → We look for causal diagnosis and therapy → Causal or empiric therapy
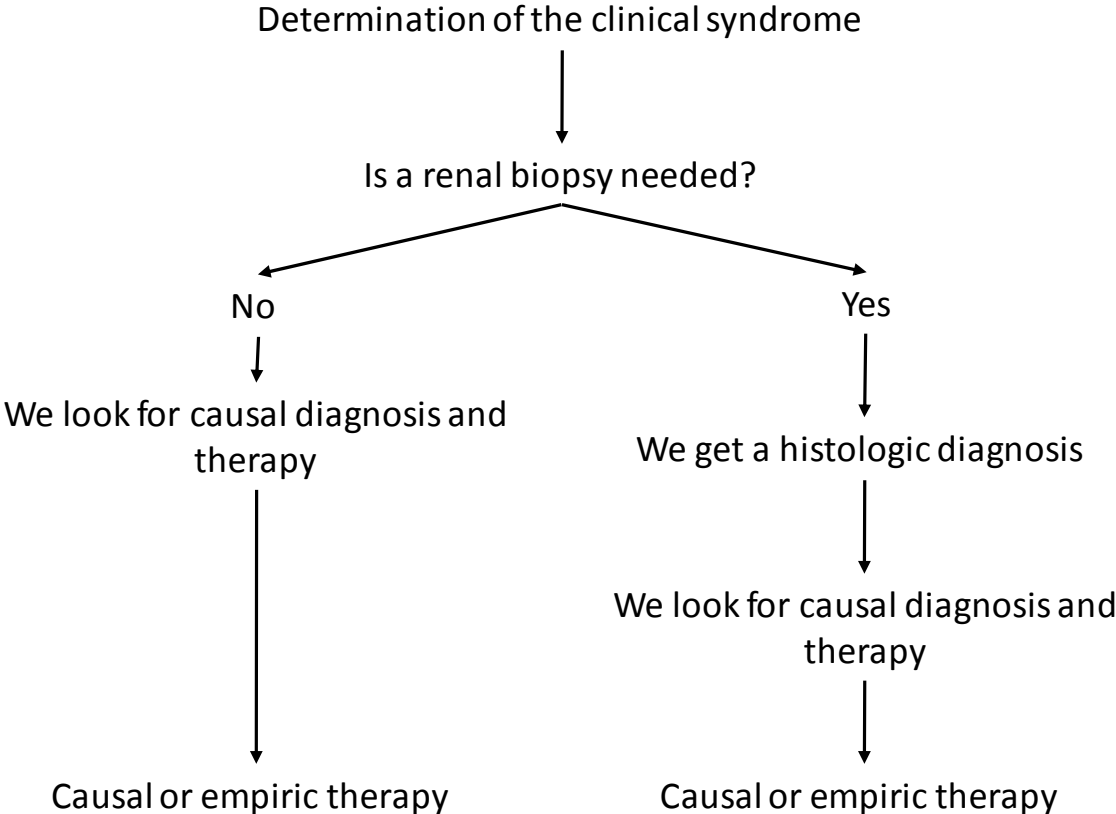
Figure: Elaboration of a nephrological diagnosis and initiation of a therapy for the clinical syndrome.

As seen in Figure, the diagnosis of the clinical syndrome, the histology diagnosis and a causal diagnosis may be required in nephrology in order to be able to provide the therapy most suitable for the patient.

Chapter 3.
Glomerulonephritides
Dr. Tibor Kovács

Diseases affecting the kidney glomeruli (at least in part by immunopathomechanism) are collectively called glomerulonephritides despite the fact that classical inflammation (-itis) in glomeruli are not observed in all diseases. The hereditary glomerular diseases (e.g. Alport syndrome) and systemic diseases that cause non-inflammatory glomerular alterations (eg. diabetic nephropathy, amyloidosis) are discussed in other sections of the note. According to some authors, it would be preferable to use the term glomerulopathy or nephropathy. (e.g. membranous glomerulonephritis or membranous nephropathy) to describe the absence of signs of inflammation. The classification of glomerulonephritis can based on:

1. etiology,
2. pathogenesis,
3. histological alterations and
4. on the basis of the clinical picture.

These classifications are shown below, but detailed description of the disease is according to the clinical picture on the basis of the international literature.

Based on the etiology

Primary or idiopathic glomerulonephritis, when systemic or other underlying conditions cannot be resolved,

Secondary glomerulonephritis, when glomerular lesions are associated with a systemic or other underlying disorder.

- autoimmune diseases (e.g. SLE, Wegener disease, vasculitis)
- infections (e.g. *bacterial:* streptococcus β haemoliticus, *viral:* hepatitis B, C, HIV, Parvovirus B19, *Parasites:* Malaria, Schistosomiasis),
- malignancies (e.g. carcinoma – lung, gastro-intestinal, lymphoproliferative diseases)
- metabolic disorders (e.g. diabetes, atherosclerosis)
- drug-induced (e.g. gold, penicillamine, ACE inhibitors, NSAIDs).

Based on pathogenesis

- glomerular deposition of circulating immune complex or in situ formation of glomerular immune complexes,

- glomerular anti-basal membrane antibody formation
- immunopathogenesis, but where immunoglobulin, the immune complex cannot be detected.

Based on kidney histological alteration

Non-proliferative glomerulonephritides

      Minimal change nephropathy

      Focal segmental glomerulosclerosis

      Membranous nephropathy

Proliferative glomerulonephritides

      Mesangioproliferative glomerulonephritis (IgA nephropathy)

      Membranoproliferative glomerulonephritis

      Diffuse proliferative glomerulonephritis

      Crescentic glomerulonephritis

On the basis of the clinical picture

1) **Oligosymptomatic disorders** (no impaired renal function, neither hypertension nor edema):

      isolated mild proteinuria (0,5-1 gramm/day)

      isolated microscopic (glomerular) hematuria

      microscopic (glomerular) hematuria with mild proteinuria.

2) **Acute glomerulonephritis syndrome** (nephritic symptoms). Its components are: glomerular hematuria, mild (non-nephrotic) proteinuria, periorbital edema, hypertension and impairment of renal function.

3) **Rapidly progressive glomerulonephritis**: rapid loss of renal function over days or weeks, accompanied by nephritic symptoms.

4) **Chronic glomerulonephritis**: persistent proteinuria, possibly with hematuria, slow deterioration of kidney function, hypertension.

In these four different clinical pictures, in addition to microscopic hematuria may sometimes be accompanied by **macroscopic hematuria**, which usually occurs painlessly as bloody / black / coke-like urine.

5) **Nephrotic syndrome** (hypoalbuminaemia as a result of persistent proteinuria over 3.5 g / day, edema, dyslipidemia and increased risk of thrombosis) - see this in detail in the next chapter.

6) **Nephroso-nephritic syndrome:** In this case, acute nephritic symptoms can be observed together with nephrotic syndrome.

Ad 1.

Isolated proteinuria

Definition and diagnosis

The disease is characterized by mild proteinuria (<1 g / day), negative urine sediment, normal blood pressure and kidney function. *Temporary isolated proteinuria* (also called functional proteinuria) may develop in the following circumstances: *fever, increased physical activity, heart failure,* which is presumably due to the changes in hemodynamic conditions; and in young adults which is called *orthostatic ptoteinuria* (being postural, it may occur after the candidate line-up, which is attributable to increased lordosis of young people, or kidney ptosis). In orthostatic proteinuria there is no proteinura in the first morning urine, while proteinuria can be detected after regular day-time physical activity (protein amount in the urine <1g / day). Renal biopsy is performed only when complete glomerulonephritis syndrome develops, so other symptoms may also appear, such as hypertension and reduced renal function.

Treatment and prognosis

The transient, intermittent or orthostatic form of isolated proteinuria is usually referred to as a benign process and requires regular inspection only.

Glomerular hematuria with mild proteinuria

Definition

Oligosymptomatic disorders may occur with a constant or intermittent glomerular type of hematuria, possibly with mild proteinuria, but –at least in the beginning – there is no hypertension or renal impairment.

Diagnosis

These urinary abnormalities do not produce any symptoms in patients. Most often they are recognised by a simple routine urine screening test (e.g. at blood donation, yearly check-up). It is of great importance that in the case of an abnormal urine test further examination be carried out. If *glomerular hematuria* occurs *without proteinuria* thin basement membrane nephropathy (see Hereditary renal diseases section) and IgA nephropathy may be in the

background. If *glomerular hematuria* occurs *with proteinuria*, IgA nephropathy occurs the most frequently, while there is a smaller possibility of other glomerulonephritis. In such cases there is no unified position when renal biopsy should be performed. The reason for this is that in most cases the differences do not require an active specific therapy and are not prone to progression. Only the lesion responsible for the symptoms can be histologically determined.

Treatment and prognosis

If it is not complicated with hypertension or deterioration of kidney function only follow-up is recommended, and the progression is usually very slow. Renal biopsy should primarily be carried out for prognostic purposes in the event of urinary abnormalities persisting over an extended period (> 1 year), of development of hypertension or if the renal function is impaired. In these cases, the general renal protective treatment may be recommended which is discussed later.

Immunoglobulin A nephropathy (IgAN)
Definition

Chronic glomerulonephritis occurs mosrt often with symptoms of persistent or remitting glomerular (micro and / or macro) hematuria and / or proteinuria, which may occur very rarely in the form of nephrotic syndrome or also of rapidly progressive glomerulonephritis. The disease is mainly characterized with a mesangial deposition of IgA on histological examination.

Epidemiology

This is the most common form of primary glomerulonephritides (10 to 50% of cases of primary glomerulonephritis). The incidence of the disease varies in different parts of the world, partly due to genetic / environmental imparity. On the other hand, the presence / absence of urine screening programs and differences in kidney biopsy protocols may also play a role. It is most common in the countries of the Far East (e.g. Japan). In Baranya County, according to our data, the incidence of the disease is 1.9 / 100,000 population. (Tibor Vas PhD thesis 2007) The disease is more common in men (2-5: 1) and typically begins in young adulthood. In a small number of patients with IgA nephropathy it may be justified to expect some other primary disease in the background: in such cases we are talking about secondary IgAN. The main causes of secondary IgAN are summarized in the following table.

Table: Commonest causes of secondary IgA nephropathy

<u>Systemic diseases:</u>	Henoch-Schönlein purpura, SLE
<u>Rheumatologic diseases:</u>	ankylotisalo spondylitis, rheumatoid arthritis
<u>Liver diseases:</u>	liver cirrhosis (primarily alcoholic liver disease)
<u>Gastrointestinal diseases:</u>	coeliac disease, Crohn's disease
<u>Dermatological diseases:</u>	dermatitis herpetiformis, erythema nodosum

Complaints and symptoms

In approximately half of the patients (40-50%) macrohematuria occur immediately (1-3 days) after upper respiratory tract infection. This is especially true for younger patients. The oligosymptomatic form (glomerular microhematuria and proteinuria) of the disease is typical for another larger group of patients (30-50%). In a few patients the predominant clinical symptoms are nephritic syndrome (~ 5%) or rapid onset of renal failure (~ 5%).

Diagnosis

Renal biopsy is necessary for diagnosis. The deposition of IgA immunocomplexes (and complement factor 3 /C3/) in the mesangial region of the glomeruli is diagnostic through immunohistological examination. The typically light microscopic image indicates mesangioproliferative glomerulonephritis, but can vary from slight mesangial lesions to a serious extracapillary crescent proliferation. The exact pathomechanism of the disease is still unknown. The dysfunction of the body's IgA immune system may lie in the background, which is supported by the clinical observation that in most cases the disease begins, or is at least activated, after infection, usually at the upper respiratory tract. An increasing amount of data confirms the hypothesis that galactosylation is impaired in hinge region IgA1 molecules, a subset of IgA, resulting in reduced galactose and sialic acid content (under-galactosylated IgA). As a result, the IgA1 molecule physicochemical properties change, causing abnormal adhering of IgA1 molecules in the mesangial region of the glomeruli. These adherent IgA molecules may trigger the glomerular immune defence mechanisms, including the activation of a complementary system. This is supported by the similar deposition of C3, observed in every case in addition to the mesangial IgA deposition and the frequently observed IgG deposition. It is not known exactly which factors influence the intensity of defence / eliminating reaction, but the histological changes will depend on the severity of these. Because of this, histological changes may become visible through light microscopy, which influence the progression / outcome of the disease. In addition to the above-mentioned,

mesangioproliferative glomerulonephritis is the most common histological alteration, but the diagnostic criterion in all cases is mesangial IgA deposition.

Further clinical studies may be required to rule out secondary IgAN, which is also affected by the IgA immune system (e.g. celiac disease) or physiological elimination of IgA molecules (e.g. liver cirrhosis). In *Henoch-Schönlein purpura* - which typically occurs in early childhood – the extra renal manifestations of systemic (IgA) immune complex vasculitis are the leading symptoms (purpura / skin / polyarthralgia, colicky abdominal pain and gastrointestinal bleeding) which are often accompanied by kidney involvement. In addition to the causes of secondary IgA nephropathy, there may be a differential diagnostic problem for the separation from poststreptococcal glomerulonephritis, but in the latter disorder the hematuria starts 1-2 weeks after streptococcal infection, whereas with IgAN this takes place immediately after the infection (see above). Today, poststreptococcal glomerulonephritis - a consequence of the generalized antibiotic treatment – is already rarer in diseases such as IgAN.

Treatment

G*eneral renal protective treatment* may be recommended for all patients, which consists of:

- An RAAS blockade, primarily angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs)
- Keeping blood pressure around 130/80 mmHg
- Life-style changes (cessation of smoking; achieving ideal body weight; keeping dietary protein intake no more than 0,8-1,0 g/bw kg in the case of normal GFR; a low salt diet)
- The uric acid level should be in the target range
- In the case of lipid abnormalities (dyslipidaemia), the use of diet and statins.

Our data show that tonsillectomy - if the tonsils turn out to be the source of the infection - may be positive for the long-term outcome of kidney disease. A favourable role in the use of fish oil was observed by other groups. Should the patient have nephrotic syndrome, steroid therapy may be effective, while if there is a fast deterioration in GFR, immunosuppressive therapy (cyclophosphamide+steroids) should be used. Of course, in the case of secondary IgAN the treatment of the primary disease takes priority.

Prognosis

In 20-30 % of IgAN patients end-stage renal failure occurs during 20-year follow-up, which is why it is important to correctly select progressors and provide a careful follow-up. Bad prognostic signs -in addition to the severity of histological changes - appear if:

- the kidney function of the patient has already deteriorated at the time of diagnosis;
- the patient is hypertensive;
- the patient has significant proteinuria (> 1 g/day);
- the patient has NO history of macrohematuric event(s);
- the patient is a smoker;
- the patient has metabolic alterations (e.g. obesity, diabetes, hyperuricaemia, dyslipidaemia).

The natural course of the disease is summarized in the next table.

Table: The natural course of IgA nephropathy

After 20 years of the start (or diagnosis) of the disease the renal function is:

- end-stage renal failure in 20-30%,
- slowly deteriorated in 40-50 %,
- normal in 30-35 % of cases.

In about 50 % of renal transplant patients who became uremic because of IgAN, abnormal IgA deposition can be observed in the mesangium of the transplanted kidney as well, which may accelerate the deterioration of transplanted kidney function. (Relapse of IgA nephropathy in the transplant.)

Thin basement membrane nephropathy and Alport syndrome
Definition

The diseases mentioned here have clinical features similar to those to be found in IgA nephropathy. Both of them are inherited kidney diseases (For more information see the chapter on inherited kidney diseases). The characteristic symptom of thin basement membrane is hematuria (glomerular type; macro- or microhematuria), but proteinuria and hematuria are typical in Alport syndrome.

Ad 2.

Acute (glomerulo) nephritic syndrome

Characteristic clinical picture consists of:

- sudden onset

- glomerular hematuria (mentioned earlier)

- mild/moderate (but non-nephrotic) proteinuria

- periorbital oedema

- hypertension and

- deteriorated kidney function.

Main causes of acute glomerulonephritis

Infections

- acute poststreptococcal glomerulonephritis

- acute postinfectiousos glomerulonephritis (induced by other bacterials, parasites, virals)

- endocarditis

Autoimmune diseases

- vasculitis

- SLE

- Cryoglobulinaemia

- Primary glomerulonephritides

- IgA nephropathy

- Membranoproliferative glomerulonephritis

Acute poststreptococcal glomerulonephritis (acute infection-related glomerulonephritis)
Definition

Acute glomerulonephritis, which begins after 1-4 weeks of sporadic or endemic beta-hemolytic Streptococcus (or other bacterial) infection. Healing is usually spontaneous after effective antibiotic treatment.

Epidemiology

In recent decades, perhaps since the wider use of antibiotics, the classical form of the disease caused by beta-haemolytic streptococci occurs more rarely and the ratio of other

infection-related diseases (caused by *bacteria*: Staphylococcus, Pneumococcus, Legionella, and *viruses*: CMV, coxsackie, EBV or *other agents*: eg. Toxoplasmosis) has increased.

Symptoms, diagnosis and prognosis

Nephritic syndrome (sometimes with characteristic periorbital edema) occurring 1-4 weeks after infection. Attention is drawn to the disease through increased anti-streptolysin titre (in Streptococcal infection) and a decreased complement (C3) level. In the case of streptococcal infections specific nephritogenic strains lie in the background. Antibody production begins against bacterial antigen in response to acute infection. After the antibody-antigen encounter (due to some structural predisposing causes) the elimination of immune complexes is damaged, and so the circulating immune complexes adhere in the glomeruli. The deposition of immune complexes (mainly C3) can be observed typically in the subendothelial or mesangial regions, which can be recognized by the electronmicroscopic examination of the glomeruli (known as "humps"). The deposition of immune complexes provokes humoral and cellular immune response in the glomeruli, as a result of which typical endothelial and mesangial cell proliferation (diffuse endocapillary glomerulonephritis) can be observed and invasion of monocytes and lypmphocytes also develop. Cell proliferation is induced by immune complexes, causing consequential lumen stenosis in the glomerular loop. This leads to a rapid decrease in GFR, which results in sodium and water retention (edema), which in turn induces elevation in the blood pressure (hypertension).

The symptoms appear after 10 to 14 days of upper respiratory tract infections (e.g. pharyngitis), or after 3-4 weeks in case of impetigo. The difference in time can be explained by the difference in penetration gate dependent immune complex formation. Generally the abdominal ultrasound shows increased echogenecity in the slightly enlarged kidneys. A renal biopsy is not usually necessary in a typical clinical case of acute poststreptococcal glomerulonephritis. Complete recovery occurs with over 90% of children, but in 60-70% of adult cases the renal function remains impaired. A diagnostic renal biopsy can be carried out should non-typical symptoms be observed or where there is uncertain background of infection, which is usually characterized by less typical acute infection-related glomerulonephritis.

Today, acute infection-related glomerulonephritides is more frequent than the classic acute poststreptococcal glomerulonephritis described above. These symptoms can be more diverse, and so renal biopsy may often be needed for diagnosis.

Treatment

The acute phase of the illness usually lasts for 7-10 days. The appropriate antibiotic treatment cures the infection, resulting in the elimination of bacterial antigens, which is followed by elimination of immune complexes, but distinctive nephritic urine may persist for months or years. For this reason long, periodic control is suggested (kidney function, blood pressure). In addition to the antibiotics for the acute phase, symptomatic treatment is also recommended (fluid balance, blood pressure).

Endocarditis-associated glomerulonephritis
Definition

This is generated in endocarditis or in patients with a pacemaker: in other cases atrioventricular shunts used to relieve increased intracranial pressure (hydrocephalus) may become infected and cause *shunt nephritis*. The pathogenesis of endocarditis-associated GN involves the deposition of immune complexes containing bacterial antigens in the glomeruli, a mechanism similar to that proposed for posstreptococcal GN, which has been discussed earlier.

Symptoms and diagnosis

The disease must be taken into consideration in the event of fever, chills, arthralgias, or anemia with typical acute glomerulonephritic alterations (hematuria, proteinuria etc.). If the patient has a pacemaker, the infection may have been caused by the wiring.

Treatment and prognosis

Adequate antibiotic treatment usually results in complete eradication of endocarditis, with correction of serologic abnormalities, but the prognosis is significantly worse than in poststreptococcal acute glomerulonephritis.

Rapidly progressive glomerulonephritis (RPGN)

This group comprises those diseases which appear as nephritic syndrome and very quickly lead to kidney failure (within weeks, months), with extracapillary crescent formation in the histological examination. They must be separated from other causes of acute kidney failure which show a good healing tendency (e.g. acute tubular necrosis, acute poststreptococcal GN, acute renal failure caused by hantavirus infection etc.), sometimes only

possible via renal biopsy. The etiological classification of rapidly progressive glomerulonephritides is as follows:

1) Antibodies against glomerular basement membrane (aGBM-ab) induced RPGN (if also associated with pulmonary manifestations, it is called Goodpasture's syndrome)

2) Immuncomplex mediated RPGN (eg. Cryoglobulinemic vasculitis, Henoch-Schönlein purpura, IgA nephropathy)

3) Circulating antineutrophil cytoplasmic antibodies (ANCA) associated with vasculitis caused by RPGN (based on pauci immune immunohistological images)

Table: Causes of rapidly progressive glomerulonephritis

1. aGBM-ab positive RPGN and alveolar hemorrhage (Goodpasture syndrome) Anti-GBM disease (only kidney manifestation)
2. Immunocomplex mediated
infection-related GN

Autoimmune diseases
  SLE
  Schönlein-Henoch disease
  Essential cryoglobulinaemia

Primary glomerulonephritis
  IgA nephropathy
  Membranoproliferative glomerulonephritis

3. No immune deposits (pauci immune)

ANCA- vasculitis
  Microscopic polyangiitis (MPA)
  Wegener granulomatosis (GPA)
  Churg-Strauss (EGPA)

Epidemiology

The classic form of RPGN is glomerulonephritis induced by antiglomerular basement membrane antibodies (aGBM-ab), and its occurrence is 0.5 to 0.9 / 1 million inhabitants / year. However, the most common form of rapidly progressive glomerulonephritis is ANCA vasculitis. For example, the prevalence in Europe of **m**icroscopic **p**oli**a**ngiitis (MPA) and **g**ranulomatosis **p**oli**a**ngiitis (GPA – its former name was Wegener's granulomatosis) is 2.5 / 100,000 population / year, 80-90% of these disorders involving the kidney. Both anti-GBM

disease and ANCA vasculitis induced RPGN are more frequent in the Caucasian (white) population than other groups of people. A slight male dominance is typical.

Symptoms, diagnosis and differential diagnosis

The disease usually begins with nonspecific symptoms. The patients are depressed, often looking up their GP with (virus) infection-like symptoms (myalgia, arthralgia, loss of appetite, low-grade fever, back pain, etc.), and the GP even starts antibiotic treatment for infection. The basis for diagnosis of this serious disease may be the rapid development of renal failure symptoms (nausea, fluid retention, electrolyte disturbances, and hypertension) accompanied by coughing, haemoptysis and hematuria (i.e. kidney-lung syndrome). Hematuria with haemoptysis may be characteristic for a classic case of Goodpasture's syndrome, or for vasculitis with renal-pulmonary manifestations (e.g. GPA - Wegener's granulomatosis). In a case of RPGN a chest X-ray is necessary to confirm or exclude lung involvement , but often a more sensitive imaging test is necessary (CT, MRI). Leucocyturia may also be present alongside the typical nephritic alteration in urine. In the blood tests increased creatinine should be suggestive of impaired renal function, in addition to any electrolyte abnormalities, but ANA, ANCA, ds-DNA, aGBM-ab and cryoglobulin determinations can be carried out for further diagnosis. A diagnosis of 60-70% of ANCA vasculitis, 10 % of Goodpasture's syndrome, and 10 to 20% of other reasons such as Cryoglobulinemic vasculitis, Schönlein-Henoch purpura, SLE etc. may lie in the background of RPGN. It should be also noted, however, that the anti-GBM disease is not always associated with pulmonary manifestations, and this time the diagnosis is not Goodpasture's syndrome, but anti-GBM-ab kidney disease. Further complicating the picture is the fact that linear IgG positivity along the GBM characteristic of the anti-GBM-ab disease are also commonly observed in diabetes (although in this case, of course, without crescent formation), so the examination of serum anti-GBM-ab level may further assist the diagnosis, as this is always negative in diabetes. Abdominal ultrasonography can show normal or enlarged kidney size with increased reflectivity of parenchyma..

In a case of rapid decline in the kidney function urgent renal biopsy is essential both for diagnosis and for differential diagnosis.

I*mmunohistological analysis* allows us to divide cases similar to those mentioned above into three groups (see Table):

1) *linear deposition* of IgG along the glomerular basement membrane (anti-GBM ab-positive cases) – anti-GBM antibodies induced RPGN

2) *granular* - usually IgG - *depositions* in different parts of glomeruli – immunocomplex mediated RPGN

3) *absence or paucity of immunoglobulin* deposition – ANCA-vasculitis associated RPGN.

The first step in crescent formation is injury sustained to the Bowmann capsule or GBM. This may be induced directly by the anti-GBM antibodies, ANCA, or some other as yet unknown or no generally known factor(s). Due to the injury of GBM albumin, cytokines and growth factors reach the primary urine compartment and cause parietal epithelial cell proliferation irrespective of the original noxa. Proliferation or inward growing of the toward the glomerular create typical crescent-like lesions. The crescent in the glomeruli ultimately squeezes the capillary tuft, thereby reducing blood circulation, detoxification and urine excretion. Initially, the crescents continue to mostly contain cells (cellular crescent) so that gradually fibrosis may develop (fibrocellular crescent), and cause necrosis, glomerulosclerosis, later completely destroyed the glomeruli (fibrotic crescent).

Parallel with the glomerular damage, inflammation occurs around the tubules belonging to the glomeruli, which cause also irreversible damage and scarring around tubules (interstitial fibrosis). The histological description of glomeruli by light microscopy is important because active immunosuppressive therapy (see below) is only able to stop or reverse the glomerular cellular destruction in a case of cellular and/or fibrocellular crescents.

Treatment and prognosis

We can only save the kidney with rapid diagnosis - immediate completion and evaluation of renal biopsy- and in some cases it can be also life-saving (this is especially serious in cases involving lung tissues). The anti-GBM disease should be treated by *methylprednisolone, cyclophosphamide and by plasmapheresis* (to remove the circulating anti-GBM antibodies). In immune complexes mediated RPGN, if it is infection-related then *antibiotics* and *methylprednisolone* are recommended, while if it is primary glomerulonephritis or of autoimmune origin (e.g. SLE) *methylprednisolone and cyclophosphamide* should be used for the treatment. If the origin of the vasculitis of rapidly progressive glomerulonephritis, *cyclophosphamide and methylprednisolone* are recommended, or should lung manifestation and/or the demand for acute dialysis persist, then *plasmapheresis* is necessary. RPGN is a very severe disease. Full recovery is increasingly rare, but in many cases the patient's renal function stabilizes at a moderately impaired level for years. The prognosis is determined by:

- the serum creatinine at detection,

- the demand for dialysis,

- the histology - how acute / recent changes can be seen in the glomeruli (see above).

Higher serum creatinine levels and dialysis requirement indicate worse kidney outcome and higher mortality.

Chapter 4.
Nephrotic syndrome
Dr. Richárd Halmai

Definition and symptoms

  <u>**Nephrotic syndrome**</u> (NS) defined as the **proteinuria exceeds 3,5 gr/day** leading to **hypoproteinemia,** primarily **hypoalbuminemia,** is associated with marked **edema**, **dyslipidemia** and a **prothrombotic state**.

  Typically, the decreased intravascular oncotic pressure due to hypoalbuminemia (<30 gr/l) and the excessive amount of sodium and the resultant water retention of the kidneys both contribute to the development of pitting edema, showing distributions by the force of gravity over the body. Notably, all these pathomechanisms of NS determine the symptomatic treatment. Hypoproteinemia via the lowered oncotic pressure stimulates the overproduction of apolipoproteins in the liver that in conjunction with the decreased lipoprotein lipase activity lead to dyslipidemia (i.e. increased levels of triglyceride, LDL- and total cholesterol, and the absolute or relative reductions of HDL cholesterol level), as well as accelerated atherosclerosis in the long term. The urinary loss of protein C, protein S and antithrombin-III and the accompanying decreased intravascular blood volume markedly increase the risk of thrombosis.

  <u>**"Nephrotic-nephritic syndrome"**</u> (i.e. nephrotic syndrome with hematuria) is presented with **coexisting symptoms of the nephrotic and the nephritic syndrome**, including proteinuria more than 3,5 gr/day, hypoproteinemia, hypoalbuminemia, marked edema, dyslipidemia, thrombophilia, as well as glomerular type hematuria, hypertension, and decreased GFR.

  Primary NS indicates glomerular disease of the kidneys *per se* with unknown etiology, while in **secondary NS** the kidneys are affected only secondarily to certain systemic diseases or conditions.

Epidemiology

  In order, the most common causes of adult primary NS are as follows: membranous glomerulonephritis > focal segmental glomerulosclerosis > minimal change nephropathy > mesangiocapillary glomerulonephritis > other causes. The previous higher incidence of NS resulting from diabetic nephropathy has recently become less common owing to the more efficient glycemic control and widespread use of RAAS-inhibitor treatments (see also in

diabetic nephropathy section). SLE and amyloidosis may occur as uncommon causes in the background of NS.

Diagnosis

Setting up the diagnosis of NS is unequivocally based on the symptoms, complaints, and laboratory parameters. The chief complaint is almost exclusively the gradual onset of edema and its consequences within days or weeks, typically occurring as periorbital edema in the morning and pitting edema of the lower extremities in upstanding patients.

The morning dominance of symptoms may be explained by the relative increases of renal blood flow during the night, which results in increased renal function and consequently the urinary loss of proteins. The presence of "anasarca" (i.e. edema throughout the body) could be complicated by dyspnoe, orthopnoe (pleural effusion, interstitial and intraalveolar edema, bilaterally uplifted diaphragm or with modest expansion due to ascites), and maldigestion (ascites, edema of the gut).

A thrombotic event can be manifested very prematurely in certain types of NS, and so assessment of circumferences of the lower extremities, examination of the Homans sign, history taking of complaints for pulmonary embolism, and the measurement of D-dimer level are all necessary.

In severe NS presented with pronounced hypoproteinemia, there also is an increased susceptibility to a variety of different infections.

The patient complaints may include the presence of foamy urine (excessive amount of protein in the urine decreases the surface-tension), or urine which is cola-like / smoky-like in color (due to glomerular hematuria in nehrotic-nephritic syndrome). In nephrotic-nephritic syndrome, occipital headache due to higher blood pressure values, or decreased urine output due to declined GFR may also develop.

Proteinuria can be determined by urine-analysis using very simple, but unfortunately very rarely conducted tests; the urinary strip, which provides a semiquantitave result (strong positive: +++ / ++++), or the sulfosalicylic acid test (i.e. mixture of the urine with few drops of 20% sulfosalicylic acid) where the formation of milky / curdy precipitates in front of a dark background confirms strong positivity. This latter method has the benefit that it detects all types of proteins.

Besides the aforementioned laboratory findings, it is not rarmeasure that a particularly higher erythrocyte sedimentation rate (~ 100 mm/h) is measured due to the lack of serum albumin level (i.e. hypoalbuminemia).

In principle, in patients with anasarca a screening urine-analysis should be performed straight away, and in a case of massive proteinuria the patient should be immediately referred to a nephrology center for a proper diagnosis and in order to initiate adequate therapy in time.

Where primary NS is suspected the indication for renal biopsy is definitive. In cases of possibly secondary forms of NS (e.g. diabetic nephropathy; familiar nephrin deficiency, etc.) the kidney biopsy is often not required. The renal biopsy by describing the histological changes of the kidney and by narrowing the spectra of potential etiological factors helps in the recognition of the systemic disease or condition in the background, and also the clarification of renal involvement in autoimmune diseases (e.g. SLE), as well as providing data for renal prognosis.

In cases of identified malignancy, or administration of drugs before the onset of symptoms that potentially could cause NS, the conduction of kidney biopsy, being an invasive diagnostic procedure, is not obligatory; however, individual consideration is required by the nephrologist.

Differential diagnosis

Edema, which is the most important clinical sign of NS, could also develop as a consequence of cardiac insufficiency. However, swollen legs in heart failure are more pronounced during the daytime, as the low pump-functioned heart is subjected to higher workload from muscles at daytime, while it becomes partially compensated for during the night with rest, when the cardiac output is facilitated and the kidneys receive proportionally more from the circulation, resulting in the edema being emptied (nycturia). In liver cirrhosis, decreased albumin- and protein secretion and increased portal hypertension lead to the formation of edema. Other causes, such as malnutrition, malabsorption, maldigestion, protein-losing enteropathy, and hypothyreoidism are less common.

In NS, the presence of diabetic nephropathy can be suspected at least 5 years after the diagnosis of type 1 or type 2 diabetes mellitus (although in type 2 DM no accurate duration is known due to the uncertainty of the onset), and when severe (proliferative) retinopathy and poorly controlled carbohydrate metabolism are concomitantly present over years.

In young female patients showing typical clinical and physical signs and laboratory findings SLE should be considered. In cases of persistent systemic inflammation or chronic infections (rheumatoid arthritis, persistent purulent processes), multiple myeloma, and very high levels of proteinuria the underlying disease may be amyloidosis.

Among the primary glomerulonephritis forms of NS, membranous glomerulopathy typically manifests as a "pure" nephrotic syndrome where thromboembolic events are the most common. In middle-aged patients, different malignancies (mainly colorectal carcinoma, lung cancer, hypernephroma, etc.) are the most frequent etiological factors, while chronic hepatitis infections (HBV, HCV) or drug-induced NS are more infrequent and in the background.

The clinical picture in focal segmental glomerulosclerosis (FSGS) is characterized rather by nephrotic-nephritic syndrome (NS with glomerular hematuria). The minimal change disease (MCD) mostly occurs as primary nephropathy with no systemic disease in the background and in the majority of cases steroid therapy is effective.

Clinical manifestation of the rare mesangiocapillary glomerulonephritis typically involves nephrotic-nephritic syndrome. This form of glomerulonephritis still lacks effective therapy; consequently, heavy proteinuria and rapid deterioration of the kidney function denote very poor prognosis.

Therapy

The treatment of patients with NS is aimed at reducing the symptoms, preventing the related complications, promoting renal recovery and improving the quality of life through the application of complex, non-specific renoprotective therapy, including moderate salt intake (< 5 gr/day), protein intake restriction (0,8 gr/kg body weight per day + amount of the urinary protein loss), a Mediterranean-type diet to improve dyslipidemia, adequate calorie intake, and physical indulgence. The correct amount of fluid intake is determined by the severity of edema, the efficacy of the dietary and diuretic therapy, and the renal hypoperfusion due to intravascular hypovolemia and the resultant decline of the renal function. (*Nota bene:* intravascular fluid deficit should be avoided to prevent renal hypoperfusion and deterioration of renal function). Components of non-specific renoprotective therapy are as follows:

- **renin angiotensin aldosteron system inhibitors** (eventually in combination therapy)
- **statin therapy** (due to the higher cardiovascular risk and also, in part, the proteinuria-reducing effects of the statins (except for rosuvastatin !))
- **diuretics** (in combination therapy when requested: furosemid; furosemid + thiazide; furosemid + thiazide + spironolactone; furosemid + amilorid): one the one hand to eliminate the edema, while on the other to energetically save the tubular system by partially blocking the tubular functions into "sparing operation mode"; in severe cases (e.g. therapy resistant anasarca) it may be necessary to perform ultrafiltration as an

ultimate refuge, when fluid excess / edema is removed by hemodialysis therapy via a high-flow canule inserted into the central vein (the jugular vein is preferred)

- **heparin therapy (vitamin K antagonist in sustained need)** in the presence of severely reduced serum albumin level (< 25 g/l) plus at least one of the following criteria: marked proteinuria (> 10 gr/day); extreme obesity (BMI > 35 kg/m^2); a previous thromboembolic event; proven genetic thrombophilia in the family; severe heart failure (NYHA st. III-IV); recent abdominal or orthopedic surgery; persistent immobility.

The symptomatic therapy is completed by using specific treatments of the systemic disease that led to NS (e.g. diabetes mellitus, SLE, amyloidosis, hepatitis, malignancy, etc.), with discontinuation of the drug (and other harmful factors) that provoked NS, as well as immunosuppressive therapy in the primary glomerulonephritis forms of NS. Prior to initiating such cytostatic treatments the risk-benefit ratio should be considered, as it could lead to severe adverse effects and complications.

For the long term, there are several factors that may be influencing the timing and the selection of immunosuppressive therapy: these include increased susceptibility to infections due to the loss of immunoglobulins and complement factors; a low serum L-thyroxine level (i.e. hypothyreoidism with normal TSH value) due to the loss of thyroxine-binding globulin; vitamin D deficiency, hypocalcaemia and secondary hyperparathyreoidism due to the increased vitamin D excretion.

Membranous glomerulonephritis
Definition

This special form of glomerulonephritis pathophysiologically develops in response to the formation of immuncomplexes "in situ" in the glomerular basement membrane or the deposition of immuncomplexes from the circulation, both of which consequently cause GBM damage. The clinical picture characteristically appears as nephrotic syndrome, although in rare cases it may manifest as "nephrotic-nephritic syndrome".

Symptoms and diagnosis

Where nephrotic syndrome or "nephrotic-nephritic syndrome" is present, a kidney biopsy is essential, as the diagnosis can only be confirmed by histology. Primary (~ 70-80% of all cases) and secondary (~20-30%) forms of membranous glomerulonephritis are known.

The primary forms can be diagnosed when any other known (secondary) causes are excluded, which can be specifically established by verifying the phospholipase-A$_2$-receptor overexpression in the histological specimen and/or by detecting autoantibodies against phospholipase-A$_2$-receptor in the serum. By assessing the autoantibody titers, it is possible to indicate therapeutic effectivity, added to which relapses could be recognized in time.

The following secondary causes have to be excluded: infections (mainly hepatitis, malaria), drugs (primarily NSAID), malignancies (e.g. lung, gastrointestinal, hematological), and autoimmune diseases (e.g. SLE).

Therapy and prognosis

When secondary causes are excluded and primary membranous glomerulonephritis is diagnosed, an observational period of 3-6 months is recommended to "wait and see" (starting at the time of identifying the diagnosis), as spontanous remission of the disease occurs in 30% of cases; specific therapy should be introduced only afterwards, when no remission has developed. In the course of the disease spontanous remission and relapse may be variable; and spontaneous remission may occur after 1-2 years following the diagnosis, suggesting long-term development of the disease. There are exceptions where the observational period is shorter, such as when there is an extremely high level of proteinuria (>8 gr/day) at the beginning, progressively increasing proteinuria, and progressive decline in the renal function during the observational period. In these cases specific therapy should be started in advance. Patients receive complex, non-specific nephroprotective therapy (see above) from the time of the histological diagnosis.

If proteinuria - more than 4 gr/day - persists after 6 months following the initiation of non-specific therapy, an immunosuppressive treatment should be introduced that consists of the administration of methylprednisolon and an alkylating agent (mostly cyclophosphamide, less often chlorambucil) for an average of half a year of period. At baseline, methylprednisolon is given intravenously at a higher dose of bolus; this is followed by maintaining oral therapy with gradually reduced dosages. Cyclophosphamide is given in one bolus per month parenterally for 6 months. This combined half-year immunosuppressive therapy is considered successful when the degree of proteinuria is clearly decreasing (< 3.5 gr/day and remains less than 50% compared to baseline values before therapy = partial remission; PR), or when it becomes almost normalized (< 0.3 gr/day = complete remission; CR) together in parallel with improved and stabilized (PR) / normalized (CR) serum albumin

level as well as stable (PR) / normalized (CR) renal function within one year after the beginning of the immunosuppressive treatment.

Further therapeutic options may include the sustained addition (for 1-1.5 years) of calcineurin inhibitors (cyclosporine or tacrolimus), when the use of methylprednisolon or cyclophosphamide is contraindicated, or combination therapy appears ineffective.

The non-specific renoprotective treatment should be applied at all times, including throughout the immunosuppressive therapy. During steroid treatment the following precautions should be taken: potassium supplementation, the prevention of gastrointestinal side effects using proton-pump inhibitors, and the prevention of osteoporosis with calcium and vitamin D supplementation. Vitamin D may also have beneficial effects on renal disease.

As proteinuria is the most significant and modifiable factor determining progression, the primary goal of the therapy is to reduce proteinuria. If proteinuria decreases below the subnephrotic range and the renal function stays stable within the normal range, the 10-year risk of end-stage renal insufficiency is comparable to that seen in the normal population. In contrast, if proteinuria remains within the range of 4-8 gr/day, the risk of end-stage renal failure increases to 50%, and with proteinuria over 8 gr/day the risk is even higher (~ 65-80%). Poor prognosis, although to a lesser extent, is also determined by male gender, elder age, and already impaired renal function at the beginning. The persistence of nephrotic syndrome, in addition to the complications of thromboembolism, increases the risk of infection and leads to accelerated atherosclerosis in the long term.

Focal segmental glomerulosclerosis
Definition

In that it shows typical histological alterations (focal = not every glomeruli are are affected; segmental = not all parts of the glomerulus exhibit sclerosis) this form manifests for the most part as nephrotic or "nephrotic-nephritic" syndrome (in 70-80%), and less often as nephritic syndrome in the clinical picture.

Symptoms and diagnosis

Primary and secondary forms are differentiated. This form is one of those known as podocytopathies, as pathomechanisms fundamentally impact the podocytes. Typically, the primary forms develop suddenly as classic nephrotic syndrome, and histological subtypes may respond variably to therapy.

The secondary forms develop rather gradually as "nephrotic-nephritic" or nephritic syndrome, with a lower degree of proteinuria and often in the absence of edema.

Treatment and prognosis

In the treatment both of secondary forms and the underlying disease, non-specific nephroprotective therapy is recommended.

Through the use of ACE inhibitors, angiotensin receptor antagonists and mineralocorticoid receptor blockers the increased intraglomerular pressure that occurs in the remaining normal glomeruli can be effectively reduced, and thus hyperfiltration can be attenuated.

In primary forms, the specific treatment initially is steroid monotherapy, which later can be completed with cyclosporine, cyclophosphamide, or mycophenolate mofetil when steroid resistance (= proteinuria does not decrease after 12 weeks of treatment with appropriate steroid dosages) or steroid dependence (= relapse develops after the discontinuation of steroid treatment by two-times consecutively) occurs.

In many patients with primer FSGS, the presence of what is known as a circulating permeability factor in the sera (putative soluble urokinase plasminogen activator receptor) can be detected which may explain why re-activation of this disease occurs relatively often in the transplant kidney graft.

Minimal change disease
Definition

This form is characterized by negative findings of immunhistology and light microscopy showing no pathological changes, and is therefore termed as "minimal change" (= minimal histological abnormalities). However, fusion of the podocyte foot processes can be observed through the use of electronmicroscopy. The clinical picture is "pure" nephrotic syndrome.

Symptoms and diagnosis

Kidney biopsy and histological examination, which is conducted due to the clinical picture of primary NS, evidently supports the diagnosis. The primer forms compass 90% of all cases, while only 10% of cases are related to secondary forms.

Treatment and prognosis

Therapy of secondary forms is required to include the treatment of underlying conditions and diseases (e.g. related to Morbus Hodgkin; lithium therapy, NSAID) and also the non-specific renoprotective treatment.

In primary forms, besides the non-specific nephroprotective treatment, specific therapy with oral steroid monotherapy is recommended: at a dose of 1 mg/bw kg until achieving complete remission (CR) up to a maximum of 4 months, followed by maintaining therapy with gradually reduced steroid dosages over the next 6 months.

Spontaneous remission in minimal change disease is very rare, thus prevention of the potential complications of NS (i.e. accelerated atherosclerosis in part by dyslipidemia, infections, thromboembolism) has to be pursued.

In response to steroid monotherapy 75% of patients are able to attain complete remission; however, relapse subsequently develops in 50% of patients.

Although acute kidney injury may develop in minimal change disease, this is usually reversible; in cases of persistent renal insufficiency other underlying causes have to be found.

The addition of cyclophosphamide or cyclosporine may be applied when steroid therapy is contraindicated at high-dose level (e.g. poorly controlled glycemia in diabetes mellitus, psychiatric disease, severe osteoporosis, etc.) or the steroid therapy seems inefficient (i.e. steroid resistance exists).

In one third of patients diagnosed with steroid dependent minimal change disease rebiopsy may be necessary, as the first kidney biopsy specimen may not contain representative tissue showing the sclerotic lesions specific to FSGS, for example (focal disease = not all glomeruli are sclerotic!) and only normal glomeruli are injected by needle at the outset. In steroid-dependent cases the use of combination therapy with cyclophosphamide or cyclosporine is recommended for improving treatment efficacy and reducing the need for steroids.

Membranoproliferative (mesangiocapillary) glomerulonephritis
Definition

In membranoproliferative (mesangiocapillary) glomerulonephritis the clinical picture shows chronic nephritis, nephrotic syndrome, or "nephrotic-nephritic" syndrome, and the histological changes involve cell proliferation and basement membrane abnormalities. Both primary and secondary forms are known, as are (based on histological findings) several subtypes.

Symptoms and diagnosis

Patients exert the symptoms of nephritic and/or nephrotic syndrome by which kidney biopsy always establishes the diagnosis. In primer forms, detecting the lower complement levels is a significant element in making the diagnosis.

Treatment and prognosis

There is a lack of unified consensus with regard to therapy. In moderate cases (based on histology, the degree of GFR and proteinuria) complex, non-specific nephroprotective treatment is recommended (see the membranous glomerulonephritis part for details).

Where there is poor prognosis as indicated by a severe histological picture, decreased GFR, and increasing level of proteinuria, the therapy can be complemented with aspirin or dipyridamol. In cases of nephrotic syndrome or the progressive decline of GFR, the addition of cyclophosphamide or mycophenolate mofetil, and low dosages of steroid given every other day could be introduced; however, there is no evidence of the efficacy and benefit of immunosuppressive and steroid treatment in this disease.

Chapter 5.
Diabetic nephropathy
Dr. István Wittmann

Definition

Those diabetic patients should be regarded as having diabetic nephropathy in whom there is an acceleration of loss of renal function, parallel to which they show either some stage of proteinuria (microalbuminuria, macroalbuminuria, proteinuria, nephritic syndrome); or show a decline in renal function, in the presence of normalbuminuria if the patient is on a prolonged and effective renin-angiotensin-aldosterone system (RAAS) inhibition therapy and another renal disease is not suspected; or if the renal histological examination verified signs indicating diabetic nephropathy.

Epidemiology

Approximately 40% of diabetic patients have diabetic nephropathy, and in countries with a western life-style, diabetic nephropathy is the most common cause of end-stage renal disease.

Pathogenesis

Pathogenesis: Genetic predisposition: It seems that polymorphisms of the RAAS may play a role in the development and progression of diabetic nephropathy. Those diabetic patients who concomitantly carry certain variants of aldose reductase and GLUT1 have a nine-fold elevated risk as regards diabetic nephropathy. Expression of eNOS variants may promote the development of diabetic nephropathy, the effect of which may be independent of blood pressure. According to human studies, a certain polymorphism of eNOS, in interaction with a polymorphism of methylene tetrahydropholate reductase, may increase the risk of microalbuminuria. Latter polymorphism is related to homocystein metabolism, which is related to the field of oxidative stress. According to a currently published meta-analysis, one of the polymorphisms of SOD2 decreases the risk of diabetic nephropathy by 20%. Carriers of apoliprotein E4 have a 2.25-fold risk as compared to other E alleles.

Pathogenesis: Epigenetic approach:, acetylation/deacetylation of the lysine amino acid residue or methylation/demethylation of arginin may be found to lie in the background of epigenetic changes. Both directions (acetylation/deacetylation and methylation/demethylation) of both processes (acetylation and methylation) are catalyzed by

different enzymes. Methylation is a modification that lasts longer and is more stable, but both acetylation and methylation result in activation of affected genes. Not only histone, but also DNA may be methylated, and in diabetes and chronic kidney disease there is a hypomethylation of DNA. Hyperglycaemia may lead to epigenetic changes through 'metabolic memory' to the development of diabetic complications among them to diabetic nephropathy.

Pathogenesis: Hemodynamic aspects: The evaluation of the most important factor of the hemodynamic approach, namely hyperfiltration, is impaired by methodologic problems, mainly uncertainties in the determination of GFR. The relative kinetics of renal enlargement and hyperfiltration is uncertain, but both are characteristic for the renal affection in diabetes. Possible causes of hyperfiltration include oxidative stress, an increased secretion of VEGF, the effect of insulin and an increased expression of SGLT2. As we do not have a clinical study that would be long enough, large enough, and sufficiently documenting GFR on the outcomes of GFR or albuminuria, at the moment no specific therapy is required for hyperfiltration. It may be assumed that this is also beneficially influenced by RAAS inhibition, such as in case of albuminuria, but further studies are needed to be able to say this.

Pathogenesis: Metabolic aspects: One important component of hyperglycaemia, the metabolic dysfunction in diabetes, is able to evoke intracellular glucotoxicity, which on the one hand directly damages the cells, and on the other hand is able to induce insulin resistance. Insulin resistance is able to alter the function of the podocytes (which play an important role as a filtration barrier) in a way that many alterations that are well-known in diabetes and are characteristic for diabetic nephropathy may be related to it. However, the possibility also arises that the podocyte-effect of insulin resistance may play a role in other pathologies not considered as diabetic nephropathy (e.g. obesity-related renal damage, or maybe secondary focal segmental glomerulosclerosis), or the worsening of other renal diseases (eg. progression of IgA nephropathy).

Pathogenesis: Oxidative stress approach: All types of cells are affected by free radical damage and the injury of redox regulation. It may launch different pathologic processes, depending on the regenerating effect of the given cell. Diabetes mellitus is a typical example for disorders in redox regulations, in the background of which we can mainly find the reducing property of glucose, by which an unpaired spin electron can be transferred to various molecules, thereby increasing their reactivity to an extreme value and in this way damaging cells. Free radical-derived and other effects can lead in diabetes to a tubulointerstitial hypoxia in the kidney, thereby leading to early vitamin D and erythropoietin deficiency. Activation of

the RAAS, the effects of cytokines and AGEs all lead to free radical processes on a subcellular level. Therefore, inhibition of the RAAS, the aim being to achieve a good glycaemic control, means no more at the subcellular level than normalizing the redox balance.

Pathogenesis: Non-enzymatic glycation: Non-enzymatic glycation leads to abnormal proteinuria and a decline in GFR by damaging all parts of the kidney. This is one of the leading pathophysiological factors of the development of diabetic nephropathy. Unfortunately, at the moment there are no real tools to its direct inhibition that could be used in clinical practice.

Pathogenesis: Cytokines: An increased production of pro-inflammatory cytokines can be observed in the background of subclinical inflammation. The most important roles are played in diabetic nephropathy by TNF-alpha and the profibrotic TGF-beta.

Pathogenesis: Renin-angiotensin-aldosterone system: At the organ-tissue level the pathogenesis of diabetic nephropathy is dominated by the activation of RAAS. The activation of RAAS can always be found in the background of insulin resistance, oxidative stress, non-enzymatic glycation, hypoxia, hyperfiltration, and cytokine effects,. Hyperglycaemia and AGEs are able to activate the RAAS by themselves.

Histology

No renal biopsy is carried out in the likelihood of diabetic nephropathy; the diagnosis must be set clinically. Glomerular damage related to diabetic nephropathy comprise thickening of the GBM, mesangial expansion, Kimmelstiel-Wilson-type nodular glomerulosclerotic lesion and marked glomerulosclerosis. This may be complemented by tubulointerstitial and vascular lesions.

Diagnosis

The diagnosis of diabetic nephropathy is based on three pillars: detection of diabetes mellitus, microalbuminuria/proteinuria and GFR-loss. As provided in the definition, in the absence of histology, a rule-out diagnosis will be set. As shall be highlighted in the detailed description of clinical course, today the absence of microalbuminuria/proteinuria does not exclude the diagnosis of diabetic nephropathy.

Differential diagnosis

Besides general considerations, carrying out a renal biopsy is suggested in diabetes mellitus (especially in type 2 diabetes), if the patient presents glomerular-type hematuria, or has no or only slight diabetic retinopathy (as compared to the level of renal damage), or an early onset (within 5 years of diagnosis of diabetes), if a sever (nephrotic range) proteinuria is present, or if we see an early onset and fast decline in kidney function. Haematuria may be caused by frequently coinciding urinary tract infections, malignancy, arterial or venous thrombosis/embolism and papillary necrosis. In these cases, however, a haematuria with normal morphology of the red blood cells is observed in the urine sediment, and no renal biopsy is needed.

Clinical presentation, stages and prognosis

Table: Stages of DNP

DNP stage	European staging	GFR-based staging (ml/min/1.73m^2)
Stage 1.	Normoalbuminuria, hyperfiltration	>90
Stage 2.	Normoalbuminuria, decreasing filtration	60-89
Stage 3.	Abnormal (30-300 mg/day) albuminuria, decreasing filtration	30-59
Stage 4.	Abnormal (>300 mg/day) albuminuria, decreasing filtration	15-29
Stage 5.	End-stage renal disease	<15

New phenomena in the clinical course of diabetic nephropathy: The threshold of hyperfiltration (125, 130, 135 ml/min) should be corrected because of the approx. 1 ml/min/1.73m2/year decline in the GFR above 40 years as: 125(130,135) - (age - 40).

Currently we have no data on the prognosis of patients who are normalbuminuric due to RAAS-inhibition and statin therapy but have an impaired or normal renal function. This question is always of higher clinical relevance, for although earlier we inferred that there can be no nephropathy in diabetics without abnormal albumin- and proteinuria, now we can

observe that this condition is becoming ever more frequent due to the wide use of RAAS-inhibitors and statins.

Screening for abnormal albuminuria: One measurement of albuminuria is not enough, as the intraindividual variability is large; therefore we can speak of an abnormal albuminuria, if 2 out of 3 measurements are positive. There are also causes for transient positivity, the diagnosis of abnormal albuminuria can only be set or declined, after these are ruled out. If the diabetic patient has no abnormal albuminuria, annual control is suggested. In patients with type 1diabetes, 5 years after the diagnosis of diabetes, in type 2 immediately at the diagnosis a screening for albuminuria is suggested. The term normoalbuminuria refers to an albumin amount < 30 mg in the 24-hour collected urine, or if the albumin/creatinine ratio in a non-collected urine specimen is < 3.0 mg/mmol. If no urine collection is available, the albumin/creatinine ratio should be used.

Development of abnormal proteinuria and albuminuria: the structures in the kidney that should prevent protein loss are endothelium, the glomerular basement membrane, the podocyte, and the slit membrane that is stretched between the foot processes of the podocytes. Protein can only enter the urine if the reabsorptive capacity of proximal tubular cells is exhausted.

Significance of abnormal proteinuria and albuminuria: In cases of patients with abonormal albuminuria, in addition to the renal disease itself dyslipidaemia, obesity, hypertension, micro- and macrovascular complications should also be screened.

Measurment of albuminuria: Nowadays albuminuria is detected using routine immunological methods, such widespread methods include immunonephelometry and immunoturbidimetry.

Factors influencing albuminuria measurement: Positional, that is postural, otherwise known as orthostatic proteinuria can occur. The clinical significance of this entity is debated. Clinically overt urinary tract infections, most inflammatory diseases, acute febrile states, physical exercise, heart failure, and dietary protein load may induce transient proteinuria. In the case of stored urine samples – even at -80°C storage – we have to face the possibility of obtaining a lower result.

Factors determining progression of albuminuria: Higher albuminuria, higher HbA_{1c}, the mean arterial pressure (MAP) value, cardiovascular disease in the family history,

hypertension, smoking, body mass and treatment of the patient are seen to be predominant in terms of determining progression of albuminuria.

Connection between blood pressure and diabetic nephropathy: While earlier guidelines set the target of less than 130/80 mmHg in the case of a proteinuria < 1 g/day, and suggested the range below 125/75 mmHg in case of a proteinuria > 1g/day, now, in the absence of data, the declared targets (< 140/90 mmHg is suggested) are more permissive. Maybe it would be more correct for us to talk about a target blood pressure range, knowing that too large a decrease in systolic and diastolic blood pressure can increase mortality. Thus the systolic blood pressure should not be lower than 100 mmHg, and the diastolic should not go below 60 mmHg. Probably here, as in all fields of medicine, an individualized therapy should be emphasized, and the target blood pressure should be determined by taking into account co-morbidities, age, gender, lifestyle, and life expectancies of patients. In order to reach the target, in general 2-4 antihypertensive medications need to be combined.

Recurrence of diabetic nephropathy after transplantation: If the diabetic nephropathy recurs in the transplanted graft kidney, then less time is needed to develop the mild damage than in the case of the native kidney. .

Connections between albuminuria and cardiovascular diseases: Renal disease and cardiovascular disease progress together in diabetic patients. The explanation for this may be the following: the same risk factors (smoking, components of the metabolic syndrome) lead to an abnormal albuminuria and renal damage, as to the development of cardiovascular diseases.

Common evaluation of GFR and albuminuria: To elaborate the risk of cardiovascular mortality and development of renal failure, albuminuria and the GFR value should be used in combination. This method has a high predictive value, is widely available and cheap.

The therapy of diabetic nephropathy

The glycaemic control of diabetes: A common statement of guidelines is that the intention to reach normoglycaemia can delay development of abnormal albuminuria in both type 1 diabetic and type 2 diabetic patients. It seems that in an established nephropathy the gylcemic control may not be as effective in slowing down the progression. While intenting euglycaemia, we should not forget that an ideal HbA$_{1c}$ range can be set up for mortality, as mortality increases both above and underneath this range. We have to try to reach values in the lower part of this range in order to decrease the risk of diabetic nephropathy.

The use of oral antidiabetic medications should be tailored individually to the GFR, while we know that gliquidone, pioglitazone, gliptins and insulin can be given at any stage of renal disease.

Inhibition of the renin-angiotensin-aldosterone system (RAAS): According to guidelines, for diabetic patients with albuminuria (in females excluding time of pregnancy) an ACEI or ARB is recommended. In cases of patients with type 1 diabetes mellitus ACE may be preferred, while in patients with type 2 diabetes, hypertension and abnormal albuminuria, ACEI and ARB may be equally effective. If these patients also exhibit a decline in GFR, ARB therapy is preferred. In cases of intolerance to ACEI or ARB, an agent from the other class should be chosen. After initiating ACEI and ARB therapy, serum creatinine and potassium measurements are eligible. Normalization of proteinuria is an important consideration in the therapy of a diabetic patient. The RAAS-inhibitor therapy should not be discontinued when the renal function becomes impaired, as it is further needed to prevent cardiovascular damage in these diabetic patients.

The order of use of antihypertensive drugs in diabetic nephropathy: The following order may be set up between antihypertensive drugs in diabetic nephropathy (numbers indicate order of choice):

1. RAAS inhibitors

2. Diuretics and/or calcium channel blockers

3. Beta-blockers (cardio selective, metabolic neutral, neutral to peripheric arterial disease; if myocardial infarct or heart failure is found in the past medical history, then use with RAAS inhibitors in the first line)

4. Central nervous system-acting or alpha$_1$-blocker

5. Direct vasodilator

Lipid-lowering therapy: Statins (except for rosuvastatin) may decrease the presence of albuminuria or proteinuria, while some studies have even described a beneficial effect in GFR-decline. Fenofibrate may significantly decrease albuminuria both in micro- and macroalbuminuria, this effect is most evident among patients with hypertriglyceridaemia, and fenofibrate also lead to a slowing down of progression of albuminuria. Moreover, it seems favourable concerning GFR loss.

The role of diet: In CKD stages 1-4, sodium intake should be below 2.3 g/day, total fat intake less than 30% of the total energy intake, saturated fatty acids less than 10% of total calorie intake, while cholesterol intake should be below 200 mg/day and carbohydrate intake should cover 50-60% of total energy intake. Protein intake in CKD 1-4 stages should be 0,8 g/day.

The role of weight loss: Weight loss could lead to a decrease in proteinuria in obese diabetic and non-diabetic patients, with GFR decreasing (if the patient is hyperfiltering) or remaining constant.

Cessation of smoking: Although no randomized, controlled study has been carried out for ethical reasons, the available data suggest that cessation of smoking may provide significant benefit in regard of the development and progression of diabetic nephropathy.

New treatment modalities verified as effective by human studies: From vitamin D and its analogues, paricalcitol has been proven to decrease the rate of albuminuria and does not cause significant adverse effects. In a meta-analysis, glitazones have shown to decrease albuminuria. In randomized, controlled trials, pentoxyphyllin has led to a significant decrease of albuminuria in patients with abnormal albuminuria (>300mg/day) (9 studies), but has proven to be inefficient in case of slighter (30-300 mg/day) albuminuria (4 studies). The existence of aldose reductase inhibitors has known and studied for 40 years; however, their effect on albuminuria has only been studied in one clinical study with patients with type 1 diabetes and abnormal albuminuria, where a significant improvement was observed. Endothelin-inhibitors, administered on top of RAAS-inhibitors, are able to decrease proteinuria, but unfortunately they increase the chance of oedema formation and one of them may lead to higher rate of heart failure. Further studies are required to weigh risks and benefits.

Chapter 6.
Ischemic Renal Disease
Dr. István Wittmann

To provide a definition of ischemic renal disease seems to be more difficult than to define diabetic nephropathy. There are certain histological findings corresponding to renal ischemia, but these are certainly not detectable during clinical diagnostic procedures. Renal biopsy is usually not indicated in these clinical settings and hence ischemic nephropathy is generally not detected.

In simple terms, ischemic nephropathy refers to stenotic alterations of the main trunk (i. e. renal artery). Although renal artery stenosis is often detected, stenotic lesions of the segmental branches are less often distinguished. Furthermore, ischemic lesions of stenotic intrarenal medium-sized arteries are not detectable by conventional radiological techniques and their histological findings also differ from the typical histological lesions of large arteries secondary to atherosclerosis.

It is believed that every little ischemic parenchymal loss leads to the impairment of the global renal function. While there are appropriate procedures to subsequent detection of small infarcts in cardiology, these procedures are generally not available in renal diseases. Hypoxia, which is injuring the heart constantly and diffusely resulting in decreased ejection fraction and diastolic dysfunction, can occur in the kidney, causing decline of GFR. Due to the lack of specific diagnostic procedures we cannot evaluate the epidemiologic, therapeutic and prognostic characteristics of ischemic renal disease.

The ischemic renal infarct secondary to renal artery embolism usually remains unrecognizable. The distinctive position of renal artery, which results in higher risk of embolism, has to be taken into consideration. Namely, renal arteries arise differently from the branching of other arteries in the body. Whereas arterial bifurcation is usually sharp-angled, the renal arteries arise from the aorta at a right-angle (Figure)

This right-angled bifurcation will result in turbulent blood flow which is consistent with the mosaic pattern on a color Doppler ultrasound. The turbulent flow increases the risk of thrombus formation, especially in conditions associated with hypercoagulability. (e.g. diabetes mellitus).
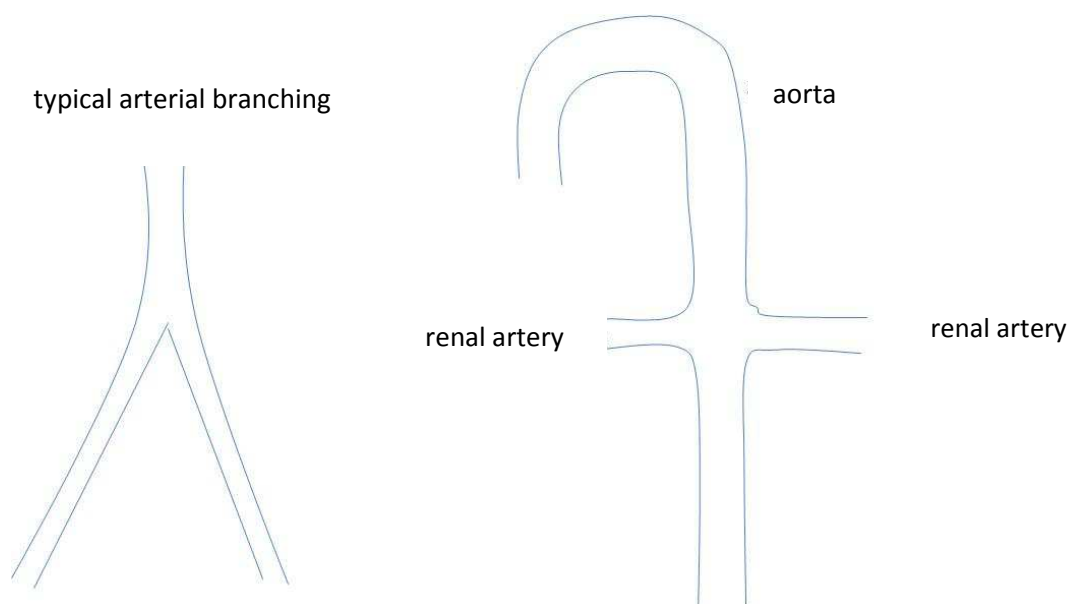
Figure: Typical arterial bifurcation and branching of the renal arteries.

Ischemic nephropathy should be considered in the following clinical settings:

1. <u>Patients with hypertensionand acute kidney injury after starting RAAS blockade</u>

   Kidney function should be rechecked within 1 week after initiating RAAS blockers. Renal artery stenosis should be considered when 30-40% increase in serum creatininand/or elevated serum potassium is observed at that control. Renal artery duplex ultrasound and usually magnetic resonance angiography are the diagnostic studies of choice, becauseCT angiography may worsen the renal function, causing contrast associated nephrotoxicity.

2. <u>Slow renal impairment (GFR decline) in patients with confirmed renal artery stenosis or other vascular diseases</u>

   Ischemic nephropathy mayliebehindrenal function impairment of elderly patients with longstanding (and/or resistant) hypertension associated with other vascular diseases (e.g. coronary heart disease, peripheral artery disease, cerebrovascular disease). If renal artery stenosis is unilateral, renal ultrasound may detect shrinkage of the affected kidney, and the contour of that kidney is usually slightly irregular. A contra lateral kidney may be hypertrophic, but in time it will also become smaller.

3. <u>Severe hypertension and/or predisposition to a sudden onset of pulmonary edema ("flush" pulmonary edema) with GFR decline.</u>

   Patients with (usually bilateral) renal artery stenosis and ischemic nephropathy may develop a sudden onset of pulmonary edemas with (although sometimes without) severe hypertension. This condition is generally associated with GFR decline.

4. <u>Atherosclerotic CKD patients, generally elderly, with acute chronic kidney injury (mostly oligoanuric AKI) as a result of total occlusion of the stenotic renal artery.</u>

Conservative (medical) treatment is the most widely recommended approach for managing (atherosclerotic) renal artery stenosis, although recommendations have often changed overthe past decade. Patients with acute renal artery occlusion or flush pulmonary edemas may benefit more from renal revascularization, and thus a revascularization procedure is the treatment of choice in patients with this clinical setting.

Chapter 7.
Renal Papillary Necrosis
Dr. István Wittmann

What is the relationship between Ludwig van Beethoven (Figure) and renal papillary necrosis?

Figure: Ludwig van Beethoven, painted by Joseph Karl Stieler (1820, Beethoven-Haus Bonn).

Ludwig van Beethoven passed away on 26 March, 1827. Anautopsy was performed by Johann Wagner andKarl von Rokitanskyon 27 March. The original autopsy report in Latin was discovered by Karl Portelein 1970 in the Vienna Museum of Anatomical Pathology. Although renal papillary necrosis was unknown in 1827 (it was first described by Friedrich in 1877), Wagner's description is so characteristic for that entity, that the diagnosis cannot be anything else. Beethovenhad been suffering from gastrointestinal symptoms. These may have been in part due to his inflammatory bowel disease, but chronic lead poisoning and liver cirrhosis secondary to his alcoholism may also have contributed to his symptoms. (Lead,

which was commonly used for improve the quality of cheap wines in the 19th century, was later detected inBeethoven's hair). His abdominal colic was probably secondary to renal papilla necrosis. He also experienced polydipsia, polyuria, extreme weight loss and slow wound healing in the last four months of his life. According to the autopsy findings he also suffered from chronic pancreatitis. His urine was not tasted; Carl August Trommer's test for the presence of glucose in urine was not in use in Vienna at that time and the van Fehling's and Benedict's urine glucose assays were first applied in 1848 and 1915 respectively, hence the assumed diabetes mellitus of Beethoven has not been diagnosed.

Based on the available data it can be declared that the famous composer suffered from renal papilla necrosis related to diabetes mellitus associated with chronic pancreatitis, but liver cirrhosis and analgesic abuse may also account for his death.

Definition

Renal papillary necrosis results from ischemic necrosis of papillae leading topapillary detachment.

Epidemiology

Usually it is elderly people who are affected. Renal papillary necrosis occurs 2-3 times more commonly in diabetic patients than in non-diabetics. The frequency of bilateral involvement is high, occurringin 50% of cases. Generally it is more common in women than in men.

Pathogenesis

Renal papillary necrosis is most frequently associated with diabetes mellitus. Further predisposing factors are as follow: sickle cell disease, urinary tract infections and obstructions, tuberculosis, liver cirrhosis, chronic alcohol consumption, analgesic nephropathy, renal transplant rejection, and systemic vasculitis. More than 50% of patients suffering from renal papillary necrosis have more than one coexisting causative factor. What is common in these factors? Renal papillary necrosis is considered to be a consequence of ischemia occurring in the renal papillae and the medulla. Therenal papilla located at the apex of each medullary pyramid also receives aphysiologicallymarginal blood supply, and each of the above mentioned underlying factors furtherimpairs that blood supply, resulting in necrosis and detachment of the papilla.

Clinical picture, diagnosis, differential diagnosis and drognosis.

Clinical presentation might be suggestive. In patients with the above mentioned underlying diseases renal colic, flank or abdominal pain, hematuria, or in severe cases (especially if renal papillary necrosis is associated with pyelonephritis) are preent, with symptoms of sepsis. Urinalysis shows hematuria with normal red blood cells (except forvasculitis, when glomerular hematuria might also be present), leucocyturia and bacteriuria. Because of the common bilateral involvement patients might also sufferbilateral flank pain. Recurrence of these symptoms may also occur; nephrolithiasis beingthe most common misdiagnosis in this situation.

Acute renal injury maydevelop, but in general the disease is manifested in slow and gradual GFR deterioration. In this setting GFR decline is partly related to the underlying disease, such asdiabetic nephropathy or chronic pyelonephritis.

Imaging procedures are essential for the diagnosis. Ultrasound is the first diagnostic test of choice, because administration ofiodinated contrast medium may contribute to further renal function deterioration or may cause contrast induced acute kidney injury. Imaging tests used by an experienced radiologist contribute to differentiation of papillary necrosis and stones as well as to an evaluation and follow-up of scarring or shrinking of the kidneys. A urologic consultation is usually necessary because urologic intervention may confirm the diagnosis or exclude other pathologies, like tumors, stones or, congenital abnormalities.

Prevention and Treatment

There are no specific preventive measures. Non-specific procedures, likemaintaining adequate volume status, preventing urinary tract infections and avoidance of nephrotoxic agents are recommended. There is no specific treatment either. Therapeutic interventions focus on optimizing fluid and hemodynamic status, controlling glycemic status, and treatment of infections with adequate antibiotic therapy. According to a case report prostaglandin E1, which improves renal circulation, may be considered a possible therapy for papillary necrosis.

Chapter 8.
Definition and classification of hypertension. Blood pressure measurement
Dr. Botond Csiky

Definition and classification of hypertension

The relationship between blood pressure values and cardiovascular events is linear and continuous: with higher blood pressure, even in the normotensive range, the cardiovascular risk increases. The threshold between physiological and pathological blood pressure values is arbitrary. Hypertension can be defined as the blood pressure value above which the benefits of the treatment are exceeding its costs.

Hypertension is defined as being when the average of a patient's blood pressure values in the doctor's examination room in a sitting position, at rest, on three different occasions (at least one week apart from each other), measured at least twice each time, are ≥140 mmHg systolic and/or ≥90 mmHgmm diastolic.

Definitions and classification of office blood pressure levels (ESH/ESC 2013):

Optimal blood pressure: <120 mmHg systolic and <80 mmHg diastolic

Normal blood pressure: 120-129 mmHg systolic and/or 80-84 mmHg diastolic

High normal blood pressure: 130-139 mmHg systolic and/or 85-89 mmHg diastolic

Hypertension:

Grade 1: 140-159 mmHg systolic and/or 90-99 mmHg diastolic

Grade 2: 160-179 mmHg systolic and/or 100-109 mmHg diastolic

Grade 3: ≥180 mmHg systolic and/or ≥110 mmHg diastolic

Isolated systolic hypertension: ≥140 mmHg systolic and/or <90 mmHg diastolic

The blood pressure category is defined by the highest level of BP, whether systolic or diastolic.

The Joint National Committee (JNC 8) classification of blood pressure:

Normal blood pressure: systolic <120 mmHg and diastolic <80 mmHg

Prehypertension: systolic 120-139 mmHg or diastolic 80-89 mmHg

Hypertension:

Stage 1: systolic 140-159 mmHg or diastolic 90-99 mmHg

Stage 2: systolic ≥160 mmHg or diastolic ≥100 mmHg

Isolated systolic hypertension: systolic ≥140 mmHg and diastolic <90 mmHg

Isolated diastolic hypertension: systolic <140 mmHg and diastolic ≥90 mmHg

Optimal blood pressure is associated with the lowest cardiovascular risk. High-normal blood pressure or prehypertension is important because at these blood pressure values the cardiovascular risk is higher than at normal or optimal blood pressure. The term prehypertension may be misleading because these persons will not necessarily become hypertensives later on. The stages of hypertension are important because with higher blood pressure the cardiovacsular risk is also increasing (although the latter is affected by comorbidities and other potential cardiovascular risk factors).

The above blood pressure values are for blood pressure measurements performed in the doctor's examination room. If self blood pressure measurement or 24-hour ambulatory blood pressure monitoring is being performed, the cut-off values for hypertension are lower.

Blood pressure measurement

Typically, blood pressure is measured on the upper arm. Wrist or finger blood pressure measurement is not recommended. In the clinical practice validated devices are used for blood pressure measurement.

It is important to use proper sized cuffs because by using a standard size cuff on an upper arm with a large circumference, higher pressure will be needed for the compression of the artery. A bladder that is too small may cause falsely high readings. If the cuff is too short or too narrow, the measured blood pressure may be 20-30 mmHg higher than the real value. For average sized adult patients (upper arm circumference 27-34 cm) a normal size adult cuff (16x30 cm) is appropriate. Larger and smaller cuffs are also available (eg. for obese patients or children).

Standard circumstances for blood pressure measurement:
- The patient should not smoke or drink beverages containing caffeine or alcoholduring the 30 minutes preceding the measurement.
- Neither the patient nor the examiner should talk during the measurement.
- The patient should be relaxed and in quiet surroundings for at least 5 minutes before the measurement (neutral conditions as regards room temperature, stress and noise, with an empty urinary bladder).
- The patient should sit comfortably with the arm supported and positioned at the level of the heart.

- The cuff should be positioned in the middle of the upper arm, placed over the brachial artery. The lower edge of the cuff should be approximately 2.5 cm above the antecubital space. The bladder should be inflated quickly to a pressure 30 mmHg above the systolic pressure recognized by the disappearance of the radial pulse (the latter shoud be determined by palpation of the radial artery).
- The bladder should be deflated relatively slowly, by 3 mmHg/s.
- Korotkoff phase I sound (appearance of the sound) representing systolic blood pressure and Korotkoff phase V sound (disappearance of the sound) representing diastolic blood pressure should be recorded.
- Blood pressure should be measured to the nearest 2 mmHg.

Home blood pressure monitoring is also important for the diagnosis of hypertension and in controlling the efficiency of the antihypertensive therapy. It involves the patient and improves adherence to medication. These measurements should also be performed under standardized conditions, typically with automatic or semiautomatic devices.

Ambulatory blood pressure monitoring (ABPM) is a non-invasive, fully automatic technique. The blood pressure is measured over a prolonged period of time, in most cases for 24 hours with an automatic device throughout an ordinary day in the patient's life.

The following entities can be diagnosed using ABPM:

White coat hypertension is defined as blood pressure that is consistently elevated by examination room readings but does not meet the criteria for hypertension based upon out-of-office readings. It is important because it can be considered as the first low-risk stage of primary hypertension.

Masked hypertension is defined as blood pressure that is consistently elevated by out-of-examination room measurements but does not meet the criteria for hypertension based upon examination room readings. It may be associated with considerably increased cardiovascular and renal risk.

Prevalence of hypertension

Hypertension is endemic. 7.1 million people die yearly because of hypertension. This is the most common medical diagnosis in the Western world.

The prevalence of hypertension is increasing; currently it is 30-45% in the adult population. In Hungary 35% of the adult population is hypertensive.

The prevalence of hypertension is affected by age, gender, obesity, diabetes mellitus, genetic factors, geographic regions, and sociodemographic factors.

Blood pressure increases with age, so the prevalence of hypertension is different in different age groups: the prevalenve is higher in older age groups. With the increased number of older people the prevalence of hypertension is also increasing.

The relationship between hypertension and gender depends on the patients' age: before menopause the prevalence of hypertension is lower in women than in men, but after the menopause it is lower in men than in women.

Obesity is a worldwide problem. The prevalence of obesity is increasing, even in childhood and in puberty. There is a tight relationship between hypertension and body weight or abdominal circumference. Not only excess, but also distribution in body weight is important: androgen (abdominal) type obesity has a stronger association with hypertension than feminine (tight-arm) type obesity.

Diabetes mellitus is also endemic and is frequently associated with hypertension. These diseases have a complex inter-relationship: jointly they are causing a dramatic increase in cardiovascular risk. In diabetics the prevalence of hypertension is higher that in the general population. In hypertensive patients the prevalence of hypertension is also higher than in the general population. In hypertensives the risk of developing diabetes is also affected by antihypertensive therapy.

The genetics of hypertension is also important. It was realised a long time ago that there is an aggregation of hypertension in certain families. In some monogenic forms of human hypertension the precise molecular mechanism has been described. In black populations the prevalence of hypertension is higher than in white populations.

Urbanization and sociodemographic factors also affect the prevalence of hypertension. In urbanized populations the prevalence is higher than in non-urbanized populations. Physical inactivity increases the risk of hypertension by 30%.

Consumption of more than 2 standard alcoholic drinks per day also increases blood pressure.

Treatment of hypertension

The goal of antihypertensive therapy is to prevent hypertensive end-organ damage and complications, to prolong the patients' life and improve the quality of life.

Who should be treated?

In general, patients with proven hypertension (blood pressure >140/90 mmHg measured repeatidly under standardized conditions) should receive pharmacological and non-pharmacological therapy. The aim of antihypertensive treatment is to decrease cardiovacsular risk. The latter is also determined by other cardiovascular risk factors and comorbidities.

How far should the blood pressure be lowered?

Blood pressure goals in hypertensive patients:

In most patients with hypertension: <140/90 mmHg.

In diabetes mellitus: <140/85 mmHg.

In very old patients (age >80 years) if the initial systolic blood pressure is >160 mmHg, than the goal systolic blood pressure is: 140-150 Hgmm.

Antihypertensive treatment consists of non-pharmacological and pharmacological treatment. Every hypertensive patient requires non-pharmacological therapy. If lifestyle changes are not sufficient to achieve the goal blood pressure, then pharmacological treatment is also needed. Pharmacological therapy is always needed if the patient has hypertensive end-organ damage, high cardiovascular risk or blood pressure > 160/100 mmHgmm.

Non-pharmacological therapy of hypertension

Non-pharmacological therapy of hypertension or lifestyle changes are important, but may only have a sufficient effect in stage I hypertensive patients who do not have other cardiovascular risk factors or comorbidities. In all other cases pharmacological therapy is also needed.

Lifestyle changes should be implemented in patients with high-normal blood pressure too, as they are also important in the prevention of hypertension.

Non-pharmacological treatment to prevent or treat hypertension and to decrease cardiovascular risk related to hypertension:

Healthy diet: rich in vegetables, fruit, low-fat diary products, whole grains and proteins from plant sources; reduced in salt, saturated fat and cholesterol (DASH diet).

Regular exercise: 30-60 min of moderate dynamic exercise on 4-7 days per week is recommended.

Moderation of alcohol consumption to no more than 20-30 g ethanol/day (<140 g ethanol/week) in males and to no more than 10-20 g ethanol (< 80 g ethanol/week) in females.

Achieving and maintaining ideal body weight: BMI 18-24,9 kg/m² (lowest mortality with BMI of 22-25 kg/m² BMI).

Waist circumference: <102 cm (males) and < 88 cm (females).

Salt restriction to < 5 g/day.

Smoke-free environment.

Blood pressure lowering effect of non-pharmacological therapy:

Intervention	Recommendation	Decrease in systolic blood pressure
Weight loss	BMI 18,5-24,9 kg/m²	5-20 mmHg/10 kg weight loss
DASH diet	see above in text	8-14 mmHg
Salt restriction	<2,4 g Na or 5 g NaCl/day	2-8 mmHg
Exercise	dynamic, min. 30 min/day	4-9 mmHg
Moderation of alcohol consumption	male < 2 "standard" drinks/day female < 1 "standard" drink/day	2-4 mmHg

Pharmacological treatment of hypertension

First choice antihypertensive drugs:

- Angiotensin-converting enzyme inhibitors (ACEIs)
- Angiotensin-II receptor blockers (ARBs)
- Calcium channel blockers
- Thiazide type diuretics
- Beta-blockers (only if they have specific indication).

In equivalent doses, other antihypertensive drugs similarly reduce the blood pressure.

In order to decrease cardiovascular risk, the most important thing is to reduce blood pressure adequately. The type of antihypertensive medication used is less important. Admittedly certain drugs may have advantages over others when specific comorbidity or end-organ damage is present.

ACEIs

ACEIs are competitive inhibitors of the angiotensin-converting enzyme. They inhibit the conversion of angiotensin I to angiotensin II and the degradation of bradikinin. As an effect the concentration of angiotensin II in the blood and in the tissues decreases, leading to a decrease in the total peripheric resistance of the arteries and to a decrease in blood pressure. They reduce left ventricular hypertrophy, improving diastolic relaxation of the heart and the coronary circulation. They have a beneficial effect in restoring "remodelling" in the peripheral arteries of hypertensive patients.

They have a proven cardiovascular preventive effect: they reduce cardiovascular and total mortality, the incidence of stroke, sudden cardiac death, hospitalization due to instable angina or heart failure, the need for revascularization and the likelihood of developing new diabetes.

In the kidneys they reduce intraglomerular pressure and through this the degree of proteinuria. These are metabolically neutral.

Side effects: in bilateral (or unilateral if the patient has a single kidney) renal artery stenosis (usually reversible), a worsening of kidney function may occur. In these cases the serum potassium level is also increased.

In renal failure or in severe heart failure it may lead to the worsening of renal perfusion, a decrease in intraglomerular pressure and through this a fast decline in the kidney function (by the mechanism described above).

The most common side effect is a dry cough, which may be present in up to 10% of patients. The mechanism is an increased bradikinin level as a consequence of the ACEI therapy. Replacing the drug with another ACEI typically does not help to stop coughing. Replacing the ACEI with an ARB resolves the problem.

Angioneurotic edema is a rare but severe side effect.

Co-administering ACEI with potassium sparing diuretic may lead to severe hyperkalemia.

ARBs

These molecules are specific antagonists of angiotensin II type 1 receptors. As a result, their effect is vasodilatation of the arterioles and decrease in peripheral vascular resistance leading to blood pressure lowering. They reduce intraglomerular pressure in the kidneys. They reduce left ventricular hypertrophy, inhibiting several steps in the process of atherosclerosis, and having a beneficial effect in heart failure and in post-myocardial patients. They also have a cardiovascular preventive effect. These drugs are metabolically neutral.

These are the first antihypertensive drugs to have placebo-like tolerability.

<u>Direct renin inhibitors</u>

This is a new group of antihypertensive drugs. They are not first choice antihypertensives; here we are purely give a short description of these medicines here for logical considerations. Aliskiren inhibits the renin-angiotensin-aldosteron system, or more exactly it inhibits activity in the circulating renin and prorenin. The effect is a reduction Level I and II in angiotensin and a reduction in plasma renin activity. Direct renin inhibitors can be used in monotherapy or in combination in the treatment of hypertension.

There have been no hard end-point clinical studies with aliskiren. It should not be given in combination with other agents blocking the RAS system in hypertension, diabetes or heart failure. Currently it is difficult to define the role of this drug in the treatment of cardiovascular diseases.

<u>Aldosterone receptor antagonists (mineralocorticoid receptor antagonists)</u>

As recent studies have demonstrated, the important role of aldosterone in the pathogenesis of primary hypertension, and the role of the aldosterone receptor antagonists in the treatment of hypertension are increasing. They are not first choice antihypertensives; we merely mention these medicines here for logical considerations as they are also inhibitors of RAAS.

Aldosterone causes salt and water retention, elevates blood pressure, promotes vascular inflammation, perivascular and myocardial fibrosis, and increases central sympathetic activity. By inhibiting the above effects, aldosterone receptor antagonists lower blood pressure and may have beneficial effects in hypertensive end-organ damage. They may be effective in the treatment of therapy resistant hypertension. Spironolactone is an old representative of these antihypertensive drugs, but has never been very popular because of its disturbing dose-dependent side effects (gynecomasty, erectile dysfunction or problems with menstruation). Eplerenon is a specific aldosterone receptor antagonist with a side effect profile similar to placebo, excepting hyperkalemia.

<u>Calcium channel blockers</u>

Acting on the L-type calcium channels of the plasma membrane, these drugs inhibitthe cells' calcium influx. This results in vasodilatation and a decrease in blood pressure. They also have anti-ischemic, anti-anginal and anti-atherosclerotic effects.

Non-dihydropyridine type calcium channel blockers (diltiazem and verapamil) reduce the heart rate, worsening myocardial contractility and slowing the conduction of the atrioventricular node.

Dihydropyridine type calcium channel blockers (amlodipine, felodipine, etc) mainly have vasodilatative effects and also improve the endothelial function. The first generation drugs, like nifedipine have slight negative effect on cardiac contractility. They act for a very short time, and so today should not be used as antihypertensives. Second generation calcium channel blockers like amlodipine have very effective vascular dilatative effects and do not depress cardiac contractility, inhibit sinoatrial or atrioventricular conduction. They are long acting. The representatives of this group are metabolically neutral.

The most common side effect of non-dihydropyridine type calcium channel blockers is bradycardia (especially if given in combination with beta-blockers, which is a prohibited combination). The most common side effects of dihydropyridines are ankle edema, flush, and headache (actually caused by overintensive vasodilatation).

Gingival hyperplasia may also occur.

Diuretics

These are among the first orally active antihypertensive drugs. Diuretics differ in structure and in major site of action within the nephron.

From this group, the most important antihypertensives are thiazides, which act by inhibiting sodium and chloride cotransport across the luminal membrane of the early segment of the distal convulted tubule (hidrochlorothiazide, chlorthalidone). While they have a weak natriuretic and diuretic effect, they also have a blood pressure lowering effect similar to the first-choice antihypertensive drugs (because they also act as vasodilatatives).

Dose dependent metabolic side effects (hyperuricemia, hyperglycemia, hyperlipidemia) limit their use. Hyperkalemia is also a common side effect. They may cause erectile dysfuntion.

Indapamide is also a thiazide-like antihypertensive. It is a sulfonamide derivate, effective antihypertensive free of metabolic side effects (when utilized in low doses).

Beta-blockers

Activation of the beta-1 receptors in the heart has a positive inotropic, chronotropic, and dromotropic effect, and causes an increase in renin outflow, lipolysis and an increase of blood presure.

All the beta-blockers are competitive inhibitors of the beta-1 receptors, but they do have different inhibitory effect on the extracardial beta-2 receptors. Beta-1 (cardio-) selective beta-blockers utilized in small doses do not have any considerable effect on beta-2 receptors and therefore have fewer side effects. Some beta-blockers are also active in peripheral alpha-blocking.

First generation beta-blockers are not selective. The representatives of the second generation are selective beta-1 receptor blockers. The third generation is a mixed group (one representative, carvedilol also acts as an alpha-blocker); their common feature is the vasodilatative effect.

Besides lowering blood pressure they have an anti-anginal, negative inotropic, chronotropic, and dromotropic effect.

Side effects: unfavourable metabolic effects on blood glucose, lipid and uric acid levels. Bronchial spasms, erectile dysfunction, and cold extremity syndrome (vasoconstriction caused by the peripheric beta-2-blocade) may occur. The above side effects are hardly ever seen when third generation or seletive beta-1 blockers are used in small doses.

Beta-blockers should only be used as first choice antihypertensives when specific comorbidities are present. Even in this case, if possible third generation beta-blockers should be chosen.

Alpha-blockers

Dilatation of the arterioles (and venules), thereby decreasing peripheral vascular resistance, can be caused by competitively inhibiting the postsynaptic alpha receptors. They provide effective relief from the obstructive symptoms of benign prostate hypertrophy. They have favourable metabolic effects.

Side effect: orthostatic hypotension. They are not first choice antihypertensive drugs.

Centrally acting drugs that lower blood pressure

These are not first choice antihypertensive drugs. Alpha-methyldopa is a central alpha-2 adrenoreceptor antagonist. Nowadays it is used only for the treatment of hypertension in pregnancy.

It is short acting and has several side effects: it may be hepatotoxic and in some patients Coombs positivity may develop.

The imidazolin I-1 receptor antagonists lowering blood pressure by decreasing sympathetic activity and peripheral resistance. They have favourable metabolic effects. Side effects: dry mouth, fatigue.

Direct vasodilators

Today these are not popular because of their numerous side effects. They cause arterial dilatation (and as a consequence a lowering in blood pressure), leading to an increase in the sympathetic tone and reflex tachycardia. The latter increase the oxygen demand of the myocardium. In ischemic heart disease this effect may cause ischemia of the myocardium, as well as secondary hyperaldosteronism with sodium and water retention. Reflex tachycardia and water (sodium) retention decreases the antihypertensive activity of the drug. If there is a need for direct vasodilatator administration at all, it should be co-administered with a beta-blocker and diuretic.

Antihypertensive combination therapy is needed in most cases. Logical combinations should be used. Fix combinations are also available.

Combined antihypertensive therapy may be initiated if the patient's blood pressure is higher by 20/10 mmHg than the goal blood pressure.

Therapy resistant hypertension

Definition: hypertension treated with antihypertensive medication from three different groups (one of them diuretics) with office blood pressure levels above the goal value.
The prognosis is bad. In most cases there is secondary hypertension in the background.

Chapter 9.
Secondary hypertension
Dr. Tibor Kovács

In the great majority of hypertensive patients (approx. 90% from previous data) the development of hypertension is not a result of one major pathomechanism; for this reason it has been recently defined as primary hypertension instead of using the previous term of *essential hypertension*. The growing body of diagnostic options and our knowledge on hypertension over the last decades suggests more delicate patient proportions; however, large, population-based clinical studies have not been performed in this direction. The most common causes of secondary hypertension are summarized in Table.

Table: The most common causes of secondary hypertension

- Renoparenchymal
- Renovascular
- Primary hyperaldosteronism (Conn's syndrome)
- Obstructive sleep apnoea syndrome
- Pheochromocytoma
- Cushing's syndrome, or abnormal secretion of other mineralocorticoids
- Coarctation of the aorta
- Hypo-, and hyperthyroidism, hyperparathyroidism
- Drug/substance-induced (e.g. oral contraceptives, liquorice, vasoconstrictive nasal drops, cocaine, amphetamines, gluco- and mineralocorticosteroids, non-steroidal anti-inflammatory drugs, erythropoietin, cyclosporine)
- Monogenic hypertension (e.g. Liddle sy., Gordon sy.)

Secondary hypertension characteristically shows a biphasic occurrence. Although it could be recognized at any age, it should be acknowledged in particular in cases of early manifestation in childhood and young adults (< 35 years), and the new onset of hypertension or the sudden worsening of high blood pressure in those above the age of 60 years. Subsequent investigations should be considered on the basis of findings of the medical history and the physical examination (see also the section of 'examination of the hypertensive patient'). *According to the recommendations (and also our own experiences) it is not necessary to conduct complete hormone screen and imaging tests in all (young) patients who*

are suspect for secondary hypertension, to which inexperienced colleagues are often inclined. Those forms of secondary hypertension which are not related closely to the kidney are subjects of other medical disciplines (endocrinology, cardiology), and thus are not discussed here.

Renoparenchymal disease and hypertension

The kidney function has a key role in regulating the blood pressure - we only have to mention water and sodium excretion, or the renin-angiotensin-aldosterone system to which we refer in more detail in previous physiological and pathophysiological studies.

From clinical aspects, it is well-known that developing / overt / poorly controlled high blood pressure considerably worsens the progression of renal diseases. In addition, there is a relatively high proportion (approx. 25%) of end-stage renal disease patients showing no other risk factor in their medical history than hypertension, which could be responsible for their kidney insufficiency.

Hypertension is an independent risk factor of the chronic kidney disease. Hypertensive patients are often presented with *abnormal urinary albumin excretion* (earlier termed as microalbuminuria) or proteinuria, already indicating damage to the glomeruli. The degree of proteinuria increases with renal impairment in hypertensive patients. Both abnormal albuminuria/proteinuria and impaired renal function are important independent cardiovascular risk factors, demonstrating a close link between renal function and hypertension.

In the centre of the vicious circle between elevated systemic blood pressure and impaired renal function, intraglomerular hypertension (a) and subsequent glomerular sclerosis (b) (scarring) have important roles.

a)

1) In systemic hypertension, vasoconstriction of the afferent arteries protects the glomeruli against increased arterial pressure. This vasoconstriction in conjunction with the decreased blood flow (due to decreased perfusion) initiates consequent pressor mechanisms, whereas the impairment of this defence mechanism (vasoconstriction) results in *intraglomerular hypertension*.

2) In renoparenchymal diseases, the loss of function as a consequence of diminished glomeruli is replaced by intact (or more unaffected) glomeruli in which, by compensating the functional deficiency, the g*lomerular pressure* increases and hyperfiltration develops.

b) In response to any of the aforementioned causes, the increased intraglomerular pressure afterwards initiates and stimulates glomerulosclerosis via several mechanisms:

    1)   Endothelial injury (release of vasoactive substances, lipid deposition, etc.)

    2)   Mesangial injury (cell proliferation, mesangial matrix accumulation)

    3)   Epithelial cell injury (proteinuria)

All the processes discussed above could result in scarring or damaging of the glomeruli, leading to further increases in blood pressure.

Several other factors could also contribute to the development of hypertension in chronic kidney disease, by being part of the aforementioned processes, and via different mechanisms: these are listed in Table.

Table: The factors increasing blood pressure in chronic kidney disease

Increased extracellular volume

Increased arterial stiffness

Activation of the renin-angiotensin-aldosterone system

Increased sympathetic activity

Reduced nephron number due to éow birth weight

Endothelin ↑, Nitric oxide ↓

Decreased production of vasodilator prostaglandins

Oxidative stress

Obesity, Insulin resistance

Sleep apnoea syndrome

Smoking

Hyperuricemia

Aldosterone-induced sodium retention and fibrosis, etc.

The incidence of hypertension varies among different renal diseases; however, the relationship between the onset of hypertension and progression of kidney disease is obvious and clear. While in minimal change nephropathy hypertension develops only in 25% of patients, this ratio exceeds 80% in FSGS. (Minimal change nephropathy < IgA nephropathy < Membranous glomerulopathies < Polycystic kidney disease < Diabetic nephropathy < FSGS)

Special aspects of antihypertensive treatment in chronic kidney disease

It cannot be emphasized enough that in hypertensive patients the most important thing is the reduction of high blood pressure itself. Based on recent available studies, target systolic pressure in patients with chronic kidney disease is lower than 140 mmHg. The reduction of systolic blood pressure below 130 mmHg is recommended only in patients with pronounced proteinuria, where GFR should be closely monitored (ESH / ESC 2013 Guideline).

Antihypertensive medications that act on the renin-angiotensin-aldosterone axis have priority in the treatment of patients with chronic kidney disease. Both ACE inhibitors and angiotensin receptor blockers (ARB) were demonstrated to possess nephroprotective effects in several multicentre, international studies. However, the cardioprotective role of ARBs appears less obvious compared to the ACE inhibitors, thus recommendations anticipate the use of small doses of ACE inhibitor therapy first and only propose the introduction of ARBs in cases of intolerance to ACE inhibitors.

Blood pressure reduction also attenuates the degree of proteinuria in patients with chronic kidney disease (intraglomerular pressure decreases). It is well-described that loss of renal function progresses more rapidly when proteinuria exceeds 1 gr/day than when remaining below 1gr/day. Unsurprisingly therefore, clinical experiences show that decreasing the blood pressure prevents the progression of kidney disease; although different antihypertensive drugs do not have equal effects.

The RAAS system inhibitors have a key role, because in addition to decreasing the blood pressure these drugs also beneficially suppress the locally activated, intrarenal RAAS system. The antiproteinuric effect of RAAS system inhibitors is therefore more pronounced in comparison with other types of antihypertensive drugs, independent of their achieving the same blood pressure reduction.

Many experimental studies on animals and smaller numbers on humans support the notion that inhibition of the intrarenal RAAS system using a combination of drugs (ACEI ± ARB ± aldosterone antagonist) could afford additional benefits in preserving the remaining renal function and reducing the higher level of proteinuria. More recent large hypertension trials have revealed that RAAS inhibition therapy combined with ACEI+ARB has increased the side effects in hypertensive patients with higher cardiovascular risk; for this reason, the combination of ACEI with ARB is not recommended solely for lowering the blood pressure and decreasing cardiovascular risk. However, for special indications, namely to reduce the proteinuria, a combination of ACEI and ARB therapy could be applied, often also supplemented with aldosterone antagonist.

Since altered sodium and water excretion plays an important role in the development of high blood pressure in patients with kidney disease or impaired renal function, the co-administration of diuretics is recommended when the target blood pressure cannot be achieved through RAAS inhibitors. The use of loop diuretics may be necessary when GFR falls below 50 ml / min.

The dihydropyridine type calcium-channel blocker nifedipine and amlodipine are less efficient in decreasing proteinuria when compared to other antihypertensive drugs, despite similar blood pressure lowering effects. In the background, unfavourable changes in the glomerular hemodynamics have been implicated; as these drugs induce vasorelaxation of the vas afferens to a greater extent than of the vas efferens leading to relative increases in intraglomerular pressure.

Chapter 10.
Gestational hypertension, preeclampsia
Dr. Tibor Kovács

In this chapter, we briefly summarize the physiological changes during pregnancy; the impact of kidney diseases on the pregnancy; the relations of gestational preeclampsia, hypertension and the kidney. Our approach to these subjects is discussed from the stance of the internalist/nephrologist, and so we also refer to gynecological textbooks and lecture materials.

Physiologic changes in the kidney during pregnancy

During pregnancy the kidney size grows by 1-1.5 cm due to increases of the RBF (renal blood flow) and interstitial fluid accumulation. In the third trimester, the dilation of the kidney cavity system and ureters may even reach the state of hydronephrosis. In the first trimester, the average blood pressure usually decreases by 10 mmHg. Hyperfiltration of the kidneys already develops by the fourth week of pregnancy, and the GFR increases, as indicated by the lower (occasionally below the lower normal value) serum creatinine level in the routine lab test.

Hypertension and pregnancy

During pregnancy, diagnosis of hypertension is considered when repeated blood pressure measurements at rest are >140/90 mmHg, similar to the blood pressure values measured in non-pregnant women. Today hypertension occurs in approx. 10% of all pregnancies. Since pregnant women are younger and the nine-month pregnancy is a physiological condition, high blood pressure over 160/110 mmHg only requires medical treatment on the basis of available data. While during pregnancy the positive impact on the mother and the infant(s) caused by treating mild/intermediate hypertension is not known. However, most recommendations suggest that drug therapy be initiated at >140/90 mmHg of blood pressure values.

Causes of elevated blood pressure in pregnancy:

1. Former, chronic hypertension (primary or secondary): hypertension is diagnosed before the pregnancy, or recognized before the 20th week of gestation that still exists for 12 weeks after delivery.

2. Gestational hypertension (pregnancy-induced hypertension): hypertension which is transient develops after the 20th week of gestation without proteinuria, and the blood pressure becomes normalized after delivery.

3. Preeclampsia: hypertension occurs after the 20th week of gestation in the presence of proteinuria (>300 mg/day).

Ad 1. (See also chapter on 'Hypertension') Pre-existing mild hypertension may be masked by reduced blood pressure that occurs during early pregnancy. In chronic hypertension, the most common maternal complication is superimposed preeclampsia.

Ad 2. It might not increase the incidence of maternal and foetal complications. In one third of patients who were initially diagnosed with gestational hypertension, progression into preeclampsia occurred with the appearance of proteinuria.

Ad 3. The precise pathophysiological mechanism of preeclampsia is still unknown, although many risk factors are well-described. Characteristic features of the clinical picture are as follows: hypertension (severe: > 160/110 mmHg, repeatedly); proteinuria (severe: > 5 g/day), and edema. In more severe cases low platelet number (< 100 000/ul), impaired liver function (elevated GOT, GPT), cerebral and visual disturbances, oliguria, and microangiopathic hemolytic anemia (elevated LDH level) could be detected. The possible consequences of preeclampsia in the mother could include hemorrhagic or ischemic stroke, ecclampsia, acute kidney injury, HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet counts), lung edema, coagulopathy (DIC), or placental abruption. Fetal complications involve intrauterine growth retardation, preterm delivery, or perinatal death.

Lowering the blood pressure during pregnancy and lactation (Table)

It is well-known that application of ACE-inhibitors, ARBs and direct renin inhibitors are all contraindicated in pregnancy. Of the Beta-blockers sustained administration of atenolol alone was reported to cause lower birth weight, but not the other types of Beta-blockers (e.g. metoprolol, oxprenolol). While some recommendations do not advise use of the entire Beta-blocker family, other recommendations differentiate between the generics and contraindicate only the addition of atenolol. In chronic hypertensive pregnant women, treatment with diuretics (thiazides) during the first trimester was shown not to increase the number of malformations, neither were perinatal adverse effects confirmed in studies.

Table: Applicable antihypertensive drugs in pregnancy

For long-term oral treatment

Methyldopa (Dopegyt) 500-3000 mg/day

Nifedipine retard 30-120 mg/day

Metoprolol 25-50 mg/day

Labetolol 200-400 mg/day

For acute treatment

Nifedipine (Cordaflex spray) 10 mg sublingual

Hydralazine 5 mg i.v. or i.m.

Urapidil (Ebrantil) 10-50 mg i.v.

Labetalol 20 mg i.v.

Nitroglycerine i.v.

The breast-feeding status should be taken into account during the post partum antihypertensive therapy. According to recommendations based on long-term clinical observations (e.g. NICE), the following drugs could be used: nifedipine, enalapril, metoprolol, and labetalol. Only traces of these drugs are excreted into the breast milk and have not shown to have any adverse effects in breast-fed infants.

Kidney diseases and pregnancy

The nephrologists meet mainly in two major forms of pregnant females:

1. In vast majority of cases, the onset of significant proteinuria after the 20th week of pregnancy is associated with preeclampsia. In some cases, however, the earlier onset (before the 20th week of pregnancy) of proteinuria or unusual dynamics of the increasing proteinuria put forward the possibility of primary kidney disease-induced preeclampsia. Thorough review of the medical history and previous medical records could extend great help in making appropriate differentiation. In the case of (heavy) proteinuria during early pregnancy, renal biopsy may be required for setting up the accurate diagnosis. In the background lupus nephropathy, minimal change, and vasculitis could be involved; and therapies of these diseases may be not accompanied by extremely increased risk in bearing out normal pregnancy.

2. In cases of pre-existing kidney disease manifested prior to the pregnancy, the chief questions are as follows:

a. How could the physiological changes during pregnancy (discussed above) affect the patient's renal function?

In patients with mild renal failure (CKD 1-2), the pregnancy usually does not or not only cause minimal deterioration of the renal function. In CKD stage 3 (eGFR 30-60 ml / min) renal function declines at the time of pregnancy in approx. 40% of patients, and the kidney function becomes recovered in approx. 50% of cases after delivery. In CKD stage 4 kidney function progressively declines with pregnancy often leading to end-stage renal failure. Nowadays, 80% of live-births could be achieved in pregnant patients who undergo renal replacement therapy due to severe renal failure that developed during pregnancy or as the consequence of pregnancy. The progressive decline in renal function could be explained by additive effects of the loss of intact glomeruli but with compensatory hyperfiltration due to the underlying kidney disease and the pregnancy-induced hyperfiltration; both of which together could augment the proteinuria, and thus further enhance the destruction and scarring of the glomeruli (glomerulosclerosis).

b. How could the kidney disease (reduced or insufficient renal function) influence the outcome of pregnancy?

The ability of women to become pregnant decreases along with the decrease in renal function, although pregnancy of women treated with dialysis is not a rarity nowadays, as the ovulation cycle in many females despite the renal failure could be more often preserved owing to improvements in the efficacy of the dialysis treatment. The worse the renal function is prior to conception; the higher the risk of intrauterine growth retardation, preterm delivery, and superimposed preeclampsia. The presence of uremic toxins and metabolic acidosis evidently harms fetal growth, although other factors may also play a part.

In summary, maternity for women with chronic kidney disease is not unfeasible nowadays; however, despite the cautious premises, the proper timing of pregnancy and the continuous monitoring of pregnant patients it is still associated with higher risk for both the mother (accelerated deterioration of renal function) and the fetus (premature birth, low birth weight).

c. How could the kidney transplantation influence the pregnancy?

The fertility potential returns to normal after six months of transplantation in young female patients. Undertaking pregnancy is recommended after 1.5-2 years of having a stable renal function. Premature spontaneous abortions are frequent (approx. 20%); although the rate of successful pregnancies increases above 90% following the first trimester. Nevertheless, these pregnancies are also commonly associated with increased risk for intrauterine growth retardation, premature birth, and superimposed preeclampsia.

Chapter 11.
Lupus nephropathy
Dr. Gergő A. Molnár

Definition

Lupus nephropathy is the renal manifestation of systemic lupus erythematosus (SLE). Regarding its pathogenesis, it is principally an immuno-complex related nephropathy that has different histological variations, each having a different prognosis.

Epidemiology

Providing an exact prevalence for SLE nephropathy is hard because of the difference in renal biopsy protocols, its possible association with other autoimmune diseases that may also have renal manifestation (e.g. Sjögren's syndrome) and the undulating activity of the disease. The disease may also already be present in 15-50% of the cases at the stage of diagnosis of SLE. Sometimes the setting up the diagnosis of SLE is aided by a renal biopsy performed as a result of renal affection of the systemic autoimmune disease showing atypical symptoms. Also, nephropathy is part of the diagnostic criteria of SLE (Table).

Table: Diagnostic criteria of SLE

1. Malar rash

2. Discoid rash

3. Photosensitivity

4. Oral or pharyngeal ulcerations

5. Non-erosive arthritis

6. Serositises

7. Nephropathy: persistant proteinuria, exceeding 0.5 g/day, or +++ using a semiquantitative test and/or cellular cylinders (containing red blood cells, hemoglobin, granular, tubular or mixed cylinders)

8. Neurologic symptoms (seizures of unexplained background or psychosis)

9. Hematologic alterations (hemolytic anemia, leukopenia/lymphopenia, thrombocytopenia)

10. Anti-DNA, anti-Sm positivity, positive anti-phospholipid test

11. Positive antinuclear test

(Based on the recommendation of the American College of Rheumatology and the protocol of the Hungarian College of Clinical Immunology and Allergology. The presence of four or more symptoms is needed to establish the diagnosis of lupus)

A clinically evident, recognized renal manifestation develops during the course of the disease at an even higher rate (35-70%). As mentioned above, indications of renal biopsy may show regional differences; moreover, after weighing up the cost/benefit ratio, many patients with light symptoms may not undergo renal biopsy. Possibly as a consequence of that, the proportion of patients with nephropathy may reach up to 90% in routine renal biopsy cohorts.

Symptoms and diagnosis

Lupus nephropathy can manifest itself in the form of different renal clinical syndromes (eg. nephrotic syndrome, acute nephritis, acute kidney injury, oligosymptomatic diease: proteinuria and/or hematuria, chronic kidney disease) (Table).

Table: Frequency of different forms of clinical presentation of SLE-nephropathy

- Proteinuria 100%
    - Nephrotic syndrome 45–65%
- Hematuria
    - Microhematuria 80%
    - Red blood cell cylinders 10%
    - Makrohematuria 1–2%
- Cellular cylinders 30%
- Impaired renal function 40–80%
    - RPGN 10–20%
    - AKI 1–2%
    - CKD 2-5. 30-60%
- Hypertension 15–50%
- Hyperkalemia 15%
- Tubular dysfunction (asymptomatic) 60–80%

(abbreviatons: RPGN: rapid progressive glomerulonephritis, AKI: acute kidney injury, CKD: chronic kidney disease, upon Feehally: Comprehensive Clinical Nephrology)

Renal affection is characterized by progressivity besides the undulating actual clinical activity; it may thereby lead to chronic kidney disease in the longer term. Suspicion of SLE-nephropathy may be raised by the onset of glomerular type hematuria, proteinuria, sterile pyuria or impairment of renal function in a known patient with a known SLE. Therefore, regular control (at least once every six months) of urine sediment, microalbuminuria/proteinuria, blood pressure and GFR is unavoidable in the diagnosis of SLE. Because of the temporal changes in the results, several urine samples should be

analyzed, if possible, besides a follow-up of clinical symptoms and activity of inflammation (eg. ESR, complement levels) results be positive (eg. proteinuria, glomerular hematuria, sterile pyuria, decrease in GFR), renal biopsy is indicated. Depending upon the result of the renal biopsy, the type of the histological variants can be detemined (eg. diffuse proliferative form, minimal alterations, RPGN), which can in turn help in providing the prognosis and how 'aggressively' the patient needs to be treated.

Table: Indications of renal biopsy in SLE
- Suspected lupus nephritis (diagnostic purpose)
  - Persistent proteinuria
  - Persistent hematuria (especially in the presence of glomerular type hematuria)
  - Persistent (sterile) pyuria otherwise not explained
  - Persistent cylindruria
  - Impaired renal function (decrease in GFR)
  - Persistent hypertension
- Worsening of parameters of renal function (choosing the therapy)
- Cases not reacting to classical therapy (choosing the therapy)
- Frequent relapses (choosing the therapy)

(According to the protocol of the Hungarian College of Clinical Immunology and Allergology)

Treatment

Treatment of SLE is mainly determined by the severity of the nephropathy; however, the presence of extrarenal manifestations (central nervous system, serositis) should also be taken into account. The percentage of fibrous, fibrocellular and cellular crescent can be provided in the case of the rapid progressive histological form (with crescents, RPGN). In the other histological forms we also have to consider the extent of already established irreversible damage (e.g. glomerular sclerosis), because in the case of severe fibrotic lesions aggressive therapy should no longer be carried out – at least not to save the renal function.

If active extrarenal manifestations or active, progressive renal manifestations are present, immunosuppressive therapy is required. Corticosteroids and cyclophoshamides (in cases of therapy resistance mycophenolate mofetil or rituximab) may be used to achieve remission. In the maintenance therapy, corticosteroids, or – in a steroid-sparing algorithm – the administration of azathioprine, cyclosporine or mycophenolate mofetil may be important. We have to try to minimize the steroid dose in maintenance therapy; additionally, the administration of potassium, vitamin D, calcium and inhibitors of proton pump is frequently needed to prevent steroid side effects. A strict diet, treatment of high blood pressure and

control of metabolic parameters are also imperative in slowing down the progression of SLE-nephropathy (just as is general in chronic kidney diseases). These aspects of treatment are also important, as SLE provides an increased cardiovascular risk that can be worsened by antiphospholipid antibodies. In the latter case or in cases with severe hypoproteinemia, vitamin K antagonist therapy may be needed because of the increased risk of thrombo-emboly.

In cases of acute or chronic renal impairment, dialysis may be needed. From the modalities of renal replacement therapies, renal transplantation can also be used in SLE-nephropathy, but the underlying disease may recur in the graft kidney. Clinically manifest SLE-nephropathy can recur in 1-30% of transplantations. Such reactivation of the disease rarely leads to graft loss. If routine biopsies are carried out in transplanted SLE patients, recurrence of SLE can be recognized in 50% of implanted grafts, but a marked proportion of these cases is not recognized due to low clinical activity.

Chapter 12.
Thrombotic microangiopathies, vasculitis
Dr. Viktória Bekő

Thrombotic microangiopathies

Thrombotic microangiopathies (TMA) are characterized by microangiopathic hemolitic anemia, thrombocytopenia and variable signs of ischaemic organ injury due to platelet thrombosis in the microcirculation. The distribution of the organ lesions varies, but the two major sites are the central nervous system and the kidney. In hemolytic-uraemic syndrome (HUS) platelet thrombi predominantly occlude the renal circulation, while in the thrombotic thrombocytopenic purpura (TTP) the main site of the ischaemia is in the brain. The incidence of TMA is low. HUS mainly affects young children, while TTP occurs more often in adults.

The central feature of TMA is endothelial damage in microvascular circulation. Injury to the endothelium is due to toxic factors (exotoxins, endotoxins, immune complexes, autoantibodies, certain drugs), especially in patient with predisposing conditions (congenital or acquired deficiencies of the complement system).

Diagnosis

The diagnosis of TMA is based on the following clinical triad.

1) Trombocytopenia is caused by platelet aggregation in thrombi of the microvascular circulation. It is more severe in TTP than in other forms. It is possible to find purpuras in the course of a physical examination.

2) Microangiopathic hemolytic anemia is due to mechanical fragmentation of erythrocytes during their passage through the narrowed vessels. In addition to the general signs of hemolysis (increased LDH, low haptoglobin level, increased indirect blilirubin level, reticulocytosis), fragmented red blood cells can be found in the peripherial blood smear. These are schistocytes with a typically helmet-like appearence. In most cases the Coombs' test is negative and coagulation factors are normal.

3) Ishaemic organ injury:

   a) acute kidney injury, predominantly in hemolytic-uraemic syndrome (often in the clinical picture of acute renal failure with anuria)

   b) central nervous system involvment in thrombotic thrombocytopenic purpura (convulsion, desorientation and other neurological deficits)

Other organ manifestations can involve the liver, gastrointestinal tract, skin and bone. A common general sign is fever.

The diagnosis of TMA is based on these clinical and laboratory findings. Renal biopsy is indicated when the diagnosis is uncertain, but severe thrombocytopaenia is a major contraindication against performing it.

Etiology

The next step after diagnosis is to find the etiology. Differentiating the various forms of TMA is important in predicting disease outcome and choosing the correct therapeutic approach.

TMA associated with infectious disease:

- acute renal failure develops within two weeks after diarrhoea caused by shiga-like toxin producing E. coli (mostly O 157:H7 serotype) or Shigella dysenteriae type 1 (diarrhoea positive, D+HUS). Exotoxin binds a receptor of the thrombocytes to the GPIIb-III and activates them. It was E. coli O104:H4 serotype that triggered the 2011 epidemic of D+HUS in Germany.
- TMA is associated with pneumococcal infection (neuroaminidase) (P-HUS)

HUS associated with genetic or immune –mediated abnormalities of the complement system: (atypical HUS, aHUS)

- Factor H deficiency (genetically determined or immune-mediated) deficiency in complement regulatory molecules leads to microvascular thrombosis
- Genetic or immun-mediated abnormalities of ADAMTS 13 (von Willebrand factor-cleaving protease). Endothel cells secrete large vWf multimers, which are cleaved by ADAMTS 13 metalloprotease. Accumulation of large von Willebrand multimers from reduced ADAMTS 13 protease activity initiate platelet aggregation and activation in the small vessels. (TTP)

Other secondary forms: associated with malignancy, autoimmun disease, HIV infection, pregnancy, drugs (e.g.: cyclosporin A, hormonal anticontraceptive, clopidogrel).

Treatment and prognosis

In all cases of TMA diagnosis is essential within a short period (24 hours), because without treatment TMA is a life threatening condition with fast progression. Supportive therapy is needed in all forms (maintaining fluid and electrolyte balance, giving transfusion and if necessary dialysis). The most effective form of treatment is plasma exchange, except in

those forms associated with infections. Daily plasmapheresis is needed until complete haematologic remission (the thrombocyte number is over 150. 000 G/l over a period of two days and there is no sign of haemolysis). In atypical HUS, if autoantibodies are present, immunsuppressive therapy (steroids, cyclophosphamide. rituximab) is administered. Eculizumab (a terminal complement inhibitor) or recombinant ADAMTS 13 are new therapeutic perspectives for the future.

Atypical HUS and TTP later can relapse. Atypical HUS progresses with up to 50% to ESRD.
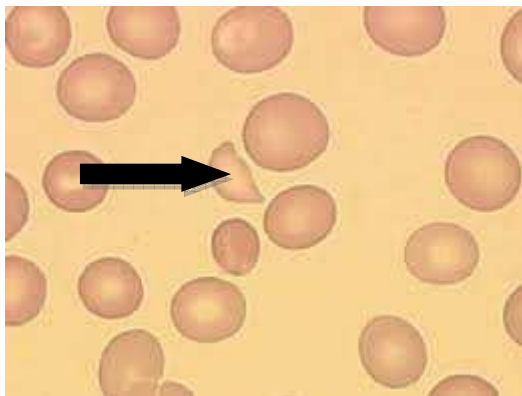
Figure: Fragmentocyte in the peripherial blood smear (arrow indicates fragmentocyte).

Vasculitis

Vasculitis is a group of diseases characterized by necrotizing inflammation of the vessels. The kidneys are often targets for systemic vasculitides. For the purposes of the classification of vasculitis, the Chapel Hill Consensus Conference definitions are used (nomenclature was revised in 2012). The basis for classification is the distribution of vessel involvement by large vessel vasculitis, medium vessel vasculitis, and small vessel vasculitis.
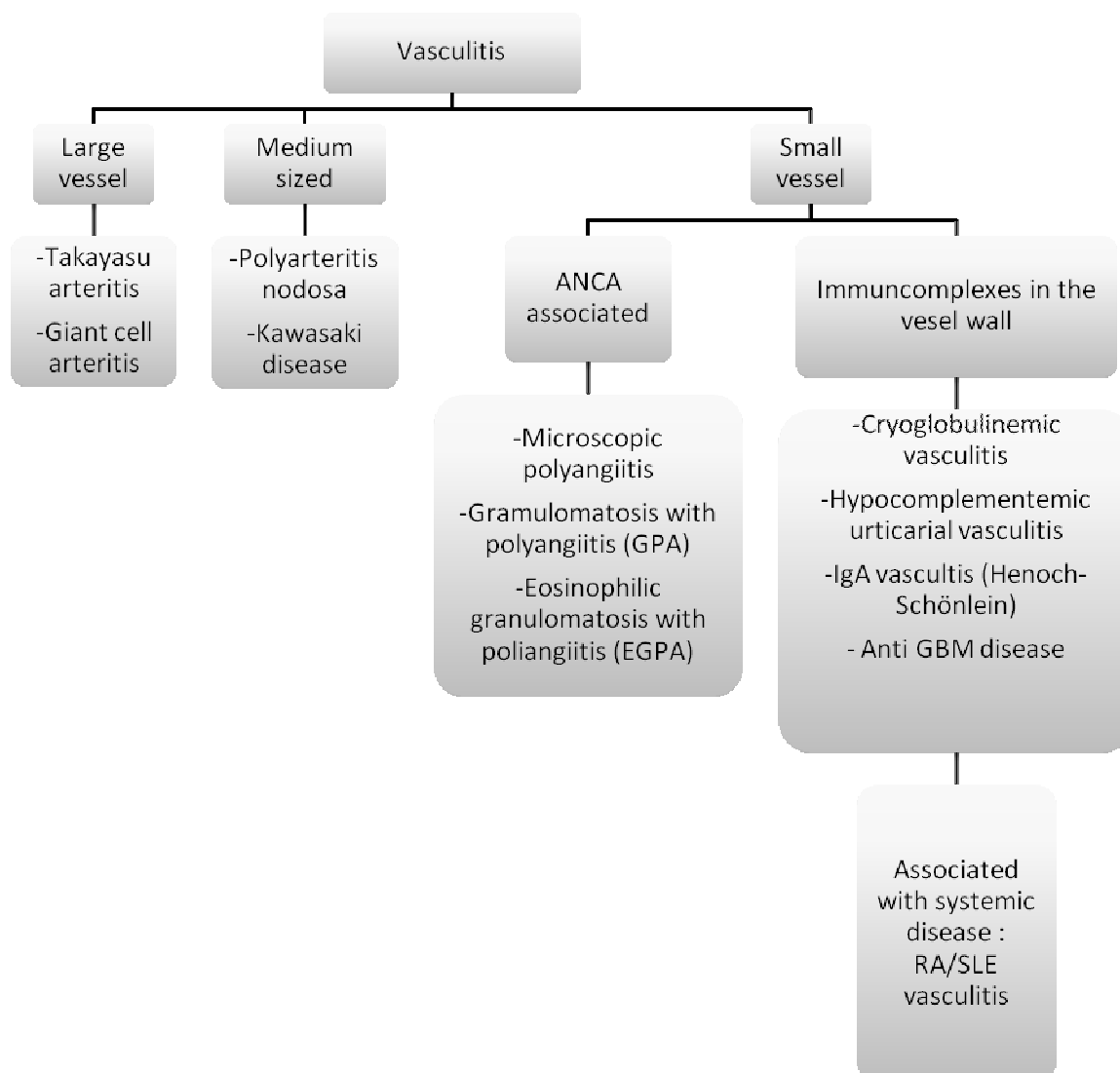
(old nomenclature: granulomatosis with polyangiitis=Wegener s granulomatosis, eosinophilic granulomatosis with polyangiitis=Churg-Strauss syndrome)

Vasculitis involving the kidneys can produce a wide variety of clinical manifestations depending upon the size of the affected vessel.

Large vessel vasculitis (aorta and beginning of renal artery)- renovascular hypertonia medium sized vessel vasculitis (renal, interlobar and arcuate arteries)-renal infarction and haemorrhage, small-vessel vasculitis (arterioles, capillaries, venules)- manifest in clinical picture of glomerulonephritis.

Here we are mainly concerned with antineutrophil cytoplasmic antibodies (ANCA) in positive small vessel vasculitis. The prevalence of this disease is approximately 1-2,5/100.000.

Clinical picture, diagnosis

The general nonspecific manifestations of systemic vasculitis involving the kidneys are fever, malaise, weight loss, and arthralgia. Renal involvement includes rapidly declining renal function, non nephrotic range proteinuria (1-3 g/die), glomerular hematuria and red cell cast.

Extrarenal manifestations mainly affect the upper and lower respiratory system (haemoptysis, dyspnoe), skin (purpuras predominantly on the lower extremities), the eye, and the gastrointestinal and central nervous system. About 10% of patients have severe pulmonary haemorrhage, which is associated with an increased risk of death. Manifestations of upper respiratory tract disease (sinusitis, rhinitis, otitis media, perforation of the nasal septum) are common in GPA/Wegener's granulomatosis. EGPA/Churg-Strauss syndrome occurs in association with bronchial asthma. Among the common laboratory findings are a high sedimentation rate, an increased CRP level, and anemia. In EGPA/Churg Strauss syndrome we find eosinophilia. Serologic testing for ANCA is a useful diagnostic procedure. About 90% of patients with small-vessel vasculitis have ANCA positivity. Two major staining patterns exist: the cytoplasmatic (c-ANCA) has a specifity for proteinase 3 found in cytoplasma of myeloid cells while the perinuclear (p-ANCA) has a specifity for myeloperoxidase (MPO). c-ANCA are most prevalent in GPA/Wegener's granulomatosis, which is positive in up to 90% of cases. Patients with EGPA/Churg-Strauss syndrome have p- ANCA. Patients with microscopic poliangiitis have a more even distribution of c-ANCA and p-ANCA.

Renal biopsy should be performed to confirm the diagnosis, given the potential toxicity of treatment. In renal biopsy crescentic glomerulonephritis with fibrinoid necrosis and lack of immunglobulin staining (pauci immun) by IF is visible. The presence of granuloma can help in differential diagnosis, but can rarely be found in a renal biopsy. Grarnulomas exclude microscopic polyangiits, because this can be found in the two other cases.

Treatment

Without therapy, ANCA vasculitis with renal involvement is associated with very poor results (e.g. one year mortality of Wegener's granulomatosis without treatment is 80%). Induction treatment consists of cyclophosphamide (0,75 g/m2 q 3-4 weeks i.v.) and steroid (pulse methylprednisolone 500-1000 mg daily x 3 days i.v, continue wiht oral prednisone 1 mg/kg/d for 4 weeks, slowly tapering down). Additional immunosuppressive therapy plasmapheresis is needed for patients requiring dialysis or rapidly increasing serum creatinin and for patients with diffuse pulmonary hemorrhage. We have to adjust the dose of immunsuppresive therapy to the renal function. In the course cyclophosphamide a continous blood count control is needed, the lowest white blood cell count occurring two weeks after the infusion. In patients who are still dialysis-dependent after three months of treatment and who have no evidence of ongoing extrarenal manifestations of active vasculitis, cyclophosphamide therapy should be discontinued. In other cases we usually continue cyclophosphamide therapy for six months.

Rituximab is a new therapeutic option, we use it now if cyclophosphamide is contraindicated or in relapse.

After remission is achieved a dosage of 1-2 mg/kg/d azathioprine is reommended for maintenance. In patients with upper respiratory disease, trimethoprin-sulfamethoxazole is used for maintenace. Patients with end stage renal diseases can receive a transplant after 12 months in complete extrarenal remission.

Chapter 13.
Tubulointerstitial nephritis
Dr. Gergő A. Molnár

Definition

Tubulointerstitial nephritis (TIN) is an acute or chronic inflammation affecting the tubulointerstitium of the kidney, usually involving cellular infiltration, functional impairment and – in the chronic form – fibrosis. The differentiation of acute vs. chronic TIN is important, as different etiological factors may be in the background, and their prognostic value is also different. Acute TIN may be – when causative therapy is applied – reversible in a certain number of cases.

Acute TIN

Epidemiology

Although a less common cause of acute kidney injury, upon renal biopsies carried out because of acute kidney injury, this may be found in 5-25% in the background of acute kidney injury. Most often (70%) it is iatrogenic, drug related; less frequently (15%) it is related to some infection, may be idiopathic (8-9%) or have other, rare causes (6%). The most frequent triggering factors are shown in *Table.*

Table: More frequent causes in the development of acute interstitial nephritides

- Medications:
    - Antibiotics
        - penicillin-derivated e.g. penicillin-G, ampicillin, methicillin
        - fluoroquinolones e.g. ciprofloxacine
        - cephalosporines (more rarely)
        - sulphonamides
        - rifampine
        - interferon
    - NSAIDs e.g. indomethacin, ibuprofene, naproxene, piroxicam
    - Diuretics e.g. thiazide, furosemide, triamterene
    - Anticonvulsives e.g. phenitoin, valproic acid, carbamazepine, diazepam
    - Antacids
        - H_2-receptor blockers e.g. cimetidine, famotidine
        - Protonpump-inhibitors e.g. omeprazole
    - Allopurinol
    - Captoprile
- Infectious agents
    - Bacteriae e.g. Legionella, E. coli, Rickettsia, Brucella, Campylobacter jejuni, Corynebacterium diphtheriae, Mycobacterium tuberculosis, Salmonella, Yersinia, Staphylococcus, Streptococcus, Leptospira

- o Viruses: e.g. Hantavírus, CMV, EBV, HBV, HIV, HAV, Adenoviridae, measles
- o Others: e.g. Chlamydia, Mycoplasma, Leishmania, Toxoplasma
- Iodine contrast media
- Autoimmune processes e.g. TINU syndrome, anti-tubular BM syndrome

Symptoms and diagnosis

Symptoms of acute kidney damage may occur, hematuria (with normal red blood cell morphology, i.e. non-glomerular), pyuria (eosinophyluria), symptoms of impairment of tubular function (non-diabetic glucosuria, aminoaciduria, acidosis, increased natriuresis, impairment of concentrating ability) may be present. In some cases, typical allergic reactions may be present (eruptions and itching of the skin, hypereosinophylia). In the infection-related form, general (fever, weakness) and specific (e.g. airway symptoms, alteration in liver function tests, thrombocytopenia) symptoms may be present. Diagnostics must involve tests of renal function, inflammatory parameters, and a qualitative blood picture. In the case of infectious symptoms, the agent may be verified using culturing or serological tests. The positive predictive value of significant (> 1%) eosinophyluria is only 30-40%, its negative predictive value is 70-75%. That is, only 30-40% of patients with eosinophyluria indeed have acute TIN, while 70-75% non-eosinophyluric patients have indeed no acute TIN. The distinct histological (but often not the etiological) diagnosis is provided by renal biopsy.

Treatment

If possible, causal therapy should be applied. In the case of medication-induced TIN, it is necessary to stop use of the drug early on, while in cases of infections, targeted antimicrobial therapy should be conducted, if possible. In case of non-infectious acute TIN, administration of corticosteroids may play a role.

Chronic TIN

Epidemiology

The exact prevalence of chronic TIN is not known. In some cases it are not recognized, and these patients may be found among those treated with renal replacement therapy because of an unknown etiology. According to estimations, they may account for 4-40% of dialysis patients; however, this data may show a large geographic variability. Most frequent cases in the background of chronic TIN are shown in *Table.*

Table: Most frequent causes of chronic TIN

- Medications and toxins:
    - Analgesics
    - NSAIDs
    - Calcineurine inhibitors
    - Herbs
    - (Heavy) metals: lithium, mercury, cadmium
    - Toxin of Balcan endemic nephropathy (aristocholic acid)
- Metabolic disorders:
    - Uric acid
    - Hypokalemia
    - Hypercalcemia
    - Hyperoxaluria
- Immune-mediated:
    - Sarcoidosis
    - Sjögren's syndrome
    - SLE
    - Rejection
- Infectious:
    - Chr. pyelonephritis
    - Hantavirus
    - Leptospirosis
- Others:
    - Multiple myelome
    - Light-chain nephropathy
    - Stone, obstruction
    - Ionizing radiation
    - Ischemia

Symptoms and diagnosis

Special forms of chronic tubulointerstitial damage involve chronic pyelonephritis (see below) and analgesic nephropathy. Frequent symptoms are (except in the case of chronic pyelonephritis) sterile pyuria, mild proteinuria, decrease in GFR, early anaemia (with a relative maintained GFR, where early decrease of erythropoietin, gastrointestinal bleeding and hemolysis in analgesic nephropathy) and papillary necrosis (see below).

Analgesic nephropathy is a special form of chronic TIN, which develops classically at year-long consumption of phenacetine, paracetamol and combined analgesics (the cumulative dose may amount to kilograms). Inhibition of vasodilatory prostaglandins and accumulation of toxic phenacetine-metabolites together lead to damage of the medullary area. In its advanced stage, small sized kidneys showing marked surface scarrings, but intact urinary space and calcification of the renal parenchyma (specifically that of the papilla) could be detected using imaging procedures. Clinically, besides symptoms typical for chronic TIN,

obstructions due to papillary necrosis or renal colic may also be present in the otherwise symptom-free patient. Further complications of analgesic nephropathy may be urinary tract cancer and an increased risk of atherosclerosis.

Therapy

If possible, the therapy should be causative, its aim being the elimination of the triggering factors (heavy metals, drugs), correction of metabolic changes, and – in cases of chronic pyelonephritis – adequate therapy of infections. Where there is an autoimmune background, immunosupressive therapy may be applied. Patients may require an early erythropoietin therapy, and end-stage renal disease can also develop early. With analgesic nephropathy, follow-ups of the patients must include surveillance for urinary tract cancer and screening for atherosclerosis as potential complications.

Contrast medium-induced nephropathy

A special form of acute tubular damage is caused by parenterally (intravenous or intraarterial) administered iodine-containing contrast media. It develops mainly in patients who already have an impaired renal function, are old, have heart failure or diabetes, or are dehydrated, and it is the third most common cause of acute kidney injury developing in hospitalized patients.

Symptoms and diagnosis

The disease may frequently be completely symptomless, so patients should be screened after contrast medium tests; that is, in cases of a high risk of contrast medium-induced nephropathy, the renal function (urine output, serum creatinine, GFR) should be re-checked after the imaging test. If the serum creatinine value increases by 25% or the GFR decreases by 20% within 72 hours of the test, contrast medium-nephropathy is suspected.

Metformin and contrast medium: Metformin is a potent antidiabetic medication; however, contraindications (such as renal impairment) should be taken into account for safe use. Contrast medium-induced nephropathy may develop more easily in diabetic patients upon using a contrast medium imaging test. This can lead to severe impairment of the renal function, and thus to cumulation of metformin, which may cause a potentially lethal lactic acidosis. Bearing that in mind, metformin should be discontinued 48 hours prior to planned contrast medium imaging tests while in cases of development of high blood glucose values

transient administration of insulin may be required. Two days after the test, the renal function sould be re-evaluated, and metformin therapy may be continued only if no renal impairment develops. In the case of acute tests such as acute coronarography there is of course no time for a cessation of metformin; in such cases the renal function should be even more closely monitored.

To prevent contrast medium-induced nephropathy, if possible low osmolarity contrast media should be used in the lowest required dose, and 2 days of 2x600 mg N-acetylcysteine may be tried orally or intravenously alongside liberal hydration from the first day of the test. The efficacy of a bicarbonate solution has not been established upon available data. If needed, both the contrast medium as well as metformin can be removed from the circulation using dialysis.

Chapter 14.
Urinary tract infections (UTI)
Dr. Tibor Vas

Definition and classification

This is the infection of the urinary tract by bacteria, fungi or parasites. **Classification of urinary tract infections** can be approached in a number of ways:

1. **Localisation:** upper- (chronic or acutepyelonephritis), and lower tract infections (cystitis, urethritis, prostatitis)

2. **Symptoms:** infections with or without symptoms

3. **Risk factors:** complicated (risk factors are present) and uncomplicated infections (no risk factors).

4. **Underlying mechanism:** ascending infections or haematogenous seeding of the urinary tract. About 95 % of UTIs are ascending infections. During this process, uropathogens (typically Escherichia coli) present in the rectal flora may form colonies around and in distal part of the urethra. After this temporary phase they enter the bladder or the upper part of the urinary tract. Smaller parts of infections (~5%) are caused by bacteriaemia with virulent bacteria (especially *Staphylococcus aureus*). Long lasting bacteriaemia or obstruction in the urinary tract are risk factors for this type of infections.

Classification from clinical point of view:

- bacteriuria without symptoms,
- acute uncomplicated cystitis of young woman
- recurrent acute uncomplicated cystitis of young woman
- acute uncomplicated pyelonephritis of young woman
- uncomplicated cystitis of adult with risk factors
- complicated urinary tract infections

Definitions

Before discussing symptoms, diagnosis and treatment of UTI-s, some definitions haveto be mentioned:

A) Pyuria, sterile pyuria, false negative pyuria

In clinical practice pyuria, sterile pyuria, and false negative pyuria can be distinguished on the basis of the underlying disease.

The importance of this classification is its diagnostic and therapeutic consequence.

1. **Pyuria:** microbiological examination of the urine is positive (bacterial infection).
2. **Sterile pyuria:** microbiological examination of the urine is negative and causes of false negative pyuria can be excluded.

   Most common causes of sterile pyuria:

   a. kidney diseases with immunological background

   b. concomitant use of antibiotics

   c. contamination with antiseptic agents

   d. gynaecological diseases (pl. colpitis)

   e. interstitial nephritis (acute or chronic)

   f. abnormalities of the urinary tract (nephrolithiasis, uroepithelial malignancies)

3. **False sterile pyuria:** In this case UTI is caused by bacteria, which is unable to grow on the usual medium (Mycoplasma, Ureaplasma, Chlamydia, Mycobacteria, fungi). Discussion among different professionals (medical staff, microbiologists) is of special importance in order to obtain the correct diagnosis.

B) Relapse, reinfection, recurrent cystitis

Relapse: the symptoms of the patient return within two weeks after the treatment and the infection is caused by the same bacteria. The infection is caused very often by a resistant bacteria, or some unknown risk factor is present. In these cases the microbiological examination of the urine is essential to identify the pathogen and obtain antibiogram, so as to be able to successfully treat the infection.

Reinfection: Symptoms return after two weeks of the successful treatment. This second, ascending infection is usually caused by pathogens (new or the same as before) from the rectal flora. The majority of cases of recurrent cystitis in otherwise healthy women result from this type of infection.

Recurrent cystitis: Symptoms of UTI-s return at least twice a year in the same patient. Detailed information about the patient's history is important. Risk factors for recurrent cystitis are previous UTI, sexual intercourse (use of spermicides), excessive use of antibiotics. In advanced years the underlying cause may be incontinence of urine or cystocele.

C) Complicated urinary tract infection

UTI is considered complicated in the following conditions: stones, tumours, obstruction, diverticuli in the bladder, fistula, neurogenic bladder, vesicoureteral reflux, catheter use, stoma, stents in the urinary tract, immune deficiencies, renal failure, previous kidney transplantation, and multiresistent pathogens. Microbiological examination of the urine is always necessary in UTIs with risk factors. We have to check for risk factors in patients with recurrent UTIs. UTIs in men are always complicated.

Epidemiology

UTIs are the most frequent of human infections. Prevalence is 4-5% in <u>women</u>, continuously increasing with age, reaching 10-20% at anolder age.

It is rare in <u>men</u> under 50 years of age (for anatomical reasons). The male: female ratio is 1:8. Parallel with the appearance of the disease of the prostate the incidence of UTIs increases even in men.

In <u>pregnant women</u> the prevalence of asymptomatic bacteriuria is 6-8%, resulting in 30-40% of cases in pyelonephritis (without treatment) and it can damage the foetus.

A higher prevalence of UTIs can be observed in infancy and childhood, probably because of the more frequent vesicoureteral reflux.

Other risk factors for UTIs: <u>concentrated urine</u> (>800 mOsm/kg), the <u>pH</u> of the urine (pH>5), <u>stasis of urine</u>, <u>kidney stones</u>, <u>proteinuria</u>, <u>haematuria</u> and <u>diabetes mellitus.</u>

Note, that in patients with fever, leucocytosis, and no clinical improvement after 2-3 days of treatment with antibiotics, resistant pathogens or other risk factors might be present.

Prevalence of pathogens causing urinary tract infections: Acute UTIs, with no risk factors or complication: The most frequent pathogen among <u>Gram negative bacteria</u> is *E.coli* (responsible for 70% of infection in the upper part of the urinary tract and ~70-95% in the lower parts).

Proteus mirabilis and Klebsiella species are responsible for 1-2% of cases, and Enterobacter, Citrobacter species and *Pseudomonas aeruginosa*for < 1% of cases.
<u>Among Gram positive bacteria,</u>the proportion of Coagulase-negative staphylococci can reach 5-20 % (or even higher), while Enterococci, *Staphylococcus aureus* and other pathogens reach no more than 1-1%.

Complicated UTIs (risk factors are present): Among Gram negative pathogens the proportion of *E. coli* decreases (~21-54 %), while that of *Proteus mirabilis* (~1-10 %), Klebsiella (2-20%), Enterobacter (2-10%), and the Citrobacter (1-5%) species increases. *Pseudomonas aeruginosa* is present in 2-20 % of cases, while in other species it is 5-20 %. Gram positive bacteria: Coagulase-negative Staphylococci: 1-4%, Enterococci 1-25%, *Staphylococcus aureus* 1-2%, others: <2%.

Special cases: The proportion of *Staphylococcus aureus*, Enterococci and Pseudomonas species is higher in urological interventions, in obstructions in the urinary tract, or in patients with kidney stones.

Mycoplasms and Ureaplasms are frequent pathogens of prostatitis and urethritis. Candida species are frequently seen in patients with catheters or in diabetic patients. Chlamydia, Trichomonasand *Neiseriagonorrhoeae* are often seen in cystitis in connection with sexual activity.

The presence of other colony-forming bacteria (Diphtheroids, lactobacilli, *Staphylococcusepidermidis)* in small number is normal.

Complaints and symptoms

The symptoms of acute cystitis comprise frequent and painful urination, acute onset of dysuria, and suprapubic pain with (non-glomerular) haematuria. Systemic symptoms such as fever are not usually present. In the presence of typical symptoms with pyuria in a patient with acute, uncomplicated cystitis no microbiological examination of the urine is necessary. Despite the typical symptoms the number of pathogens in the urine is relatively low (10^2-10^4germs/ml). A recurrent acute cystitis usually causes no permanent decrease of renal function. The most frequent pathogens are *E. coli* (~ 75-90%) and *Staphylococcus saprophyticus* (~5-15%). In UTIs caused by other pathogens, risk factors may be present.

Back pains (especially during the physical examination), high fever, shivering, nausea, leukocyturia, white blood cell casts, and macrohaematuria are characteristic of **acute pyelonephritis.** Some patients have only mild symptoms, but sometimes severe sepsis can occur. In laboratory tests leukocytosis, increased blood sedimentation rate, and a high CRP level can be found. On the other hand, sometimes the typical symptoms can be absent. In acute pyelonephritis, microbiological examination of the urine is compulsory. The mechanism of the infection is in the majority of cases of an ascending type (~95%). *Staphylococus aureus* sepsis can be caused by haematogenous feeding. The most frequent pathogen is *E.coli,*other

bacteria resident in bowels (Proteus, Klebsiella, Enterococci) may cause pyelonephritis, but it is rarely acute.

Chronic pyelonephritis often has only mild symptoms, yet recurrent acute infections can draw attention to the disease, with risk factors in the background.

In the case of dysuria, with many squamous cells in the sediment, but without pyuria and haematuria, we have to consider the presence of colpitis. The probability of cystitis in such cases is only 20 %.

Catheter-related infections: 15-25% of patients in hospitals are connected to catheters. The probability of bacteriuria increases by 3-10% every day. The catheter is the most frequent cause of Gram negative bacteriaemia. Complications arising from catheter use after ~30 days include bacteriaemia, acute cystitis, and pyelonephritis. Other complications might be a variety of multiresistant pathogens, the obstruction of the catheter, stone formation, and local genitourinal infections. The most frequent pathogens are: Proteus, Pseudomonas, Klebsiella, *E.coli,* Enterococcus species, *Staphylococcus aureus,* and Candida species. Sterile insertion is imperative, as are the avoidance or minimalization of catheter use.

Diagnosis

In addition to detailed case history laboratory tests, urine analysis, microbiological examinations maybe necessary (and sometimes compulsory) for diagnosis.

Examination of the urine sediment

By using a light microscope, bacteria, white blood cells, and sometimes (non-glomerular) red blood cells can be seen in the sediment of the urine. Should the sediment contain only bacteria but an absence of pyuria, there is probably no infection, only stale urine.

In clinical practice, in addition to the typical symptoms, white blood cells in the sediment are enough to diagnose cystitis without complications. In this case no microbiological examinations are needed. There are many ways to establish the presence of pyuria. The simplest method is the use of dipsticks. It is fast, easy, and cheap. Another method is microscopic evaluation of the urine sediment. An incidence of more than 5 white blood cells/high power field (400x) after centrifugation should be treated as pathological (sensitivity: 95%, specificity: 70%).

In the case of dysuria, when the sediment contains many squamous cells but no pyuria or haematuria, we should consider the possibility of colpitis. Gynaecological examination is needed.

According to the guidelines, if the complaints and symptoms are unambiguous, no risk factors or complications are present, and no laboratory test can be made, acute uncomplicated cystitis can be diagnosed even without microscopic evaluation of the urine sediment.

Microbiological examination

Microbiological examination using midstream voided urine is required for the precise determination of the infection (pathogen, germs/ml, drug resistance). Previously, more than 10^5germ/ml and signs of UTI wereconsidered significant. Less than 10^5germ/ml with uropathogen bacteria and clinical symptoms may be a sign of real UTI.

Imaging techniques

The following techniques may be necessary in establishing anatomical abnormalities in the background of complicated UTIs:

- Ultrasound examination, abdominal CT examine pyelectasia, obstruction (stones, tumour), to measure the size of the kidneys and visualise their surface area (smaller kidneys with a rough, uneven surface are suspicious and may indicated chronic pyelonephritis).
- Isotope examination to visualise obstruction or vesicoureteral reflux
- Urography:used on rare occasions (avoided where possible in patients with decreased renal function, because of the administration of contrast media involved). It should be used after the acute phase of the infection. It is useful for visualising stones in the pyelon, and anatomical abnormalities of the ureter.

Prevention and treatment

In addition to antibiotic treatment (see later) the appropriate enlightenment of patients is essential in prevention and successful treatment of UTIs. Patient can participate in the cure by taking the following useful measures:

- Ensuring that their fluid intake is more than 2 litres/day
- emptying the bladder before going to sleep, and after sexual activity
- taking showers rather than baths
- avoiding constipation

Indication for antibiotic treatment in asymptomatic bacteriuria: pregnancy, immunosuppression (after transplantation, receivingimmunosuppressive drugs), vesicoureteral-reflux, nephrolithiasis or before kidney biopsy.

For **uncomplicated acute cystitis** of young women a 3-4 day antibiotic treatment may be sufficient. The first line of choice: fosfomycine (1 x3 g), nitrofurantoin (4x50 mg for 7 days), pivmecilline (2x200 mg for 7 days, or 2x400 mg for 3 days, not available in Hungary) and trimethroprim-sulfamethoxazole (2x160/800 mg, for 3 days), but only in areas where the resistance of E.coliis less than 20 %. Drugs of second choice include ciprofloxacin 2x250 mg, levofloxacin 4x250 mg, norfloxacin 2x400 mg, ofloxacin 2x200 mg, cephalexin (4x500 mg), cefpodoximeproxetil 2x100 mg (3 days for each) and amoxicillin/clavulanic acid (3x375 mg for 7 days).

Longer antibiotic treatment has no beneficial effect, but there is a prevalence and number of complications in connection with antibiotic treatment. Naturally, the cost for longer treatment is higher. If there is no improvement within 3 days of treatment, further microbiological examinations, imaging techniques, urological examinations are needed to find risk factors, resistant pathogens, or other complications.

For **recurrent uncomplicated acute cystitis** of young women (where symptoms return after 2 weeks, > 2 cystitis/6 months) there are three possible treatment options:

a) Continuous small dose prophylaxis with antibiotics administered in the evenings before going to bed: trimethoprim/sulfamethoxazole (1x40/200 mg), nitrofurantoin (1x50-100 mg), cefaclor (1x250 mg), cephalexin (1x125-250 mg), norfloxacin (1x200 mg), ciprofloxacin(1x125 mg), orfosfomycin (1x3g for 10 days).

Trimethoprim/sulfamethoxazole every 2 days may be also effective. If it is effective, it can be continued for 1-2 years. The frequency of infections (2-3 UTI/year) can be decreased to 0,1-0,2 UTI/year.

b) UTI related to sexual activity can be treated with one dose prophylaxis: trimethoprim/sulfamethoxazole (1-2x40/200 mg), nitrofurantoin (1x50-100 mg), cephalexin (1x250 mg), norfloxacin (1x200 mg), ciprofloxacin (1x125 mg), orofloxacin (1x100 mg).

c) the indication for treatment (one dose or a 3 day treatment) is made by the patient itself. It is beneficial to patients who have shown good compliance, but do not want to take antibiotics continuously. Although the prevalence of UTIs will not decrease, the duration of symptoms can be reduced.

In cases of **recurrent uncomplicated acute pyelonephritis** in young women showing only mild symptoms, the oral use of antibiotics may be enough. Our drugs of first choice are ciprofloxacin (2x500-750 mg) and levofloxacin (4x250-500 mg for 7-10 days, or 4x750 mg for 5 days). Other options include cefpodoximproxetil 2x200 mg, ceftibuten 4x400 mg (10 days for each). On the basis of previous microbiological examination, cefuroxime (2x500 mg), or trimethoprim/sulfamethoxazol (2x160/800 mg, for 14 days) also can be used.

Complicated acute cystitis of young women without complications but with severe clinical symptoms (high fever, nausea, bad general condition), hospitalisation and parenteral antibiotic treatment is needed.

Because of the increasing frequency of the resistance to E.coli for fluorokinolons, drugs can only be of first choice if resistance is less than 10%. In other cases cephalosporins of the 3rd generation can be administered. For the same reason trimethoprim/sulfamethoxazol can be administered only after previous microbiological examination. In severe cases, until obtaining the result of the microbiological examination, aminoglycoside+imipenem, or aminoglycoside+carbapenem can be administered.

The parenteral antibiotics of first choice are ciprofloxacin (2x400 mg) and levofloxacin (4x250-750 mg). Alternative antibiotics include cephalosporins (cefuroxime 2-3x0,75-1,5 g; cefoxitin 2x1-2 g; cefotaxim 3x2 g; cetriaxon 1x1-2 g, ceftazidim 3x1-2 g, cefepim 2x1-2 g). Ceftazidimand cefotaximarenot preferred in monotherapy. In severe cases, gentamycin (5 mg/kg 4 times a day) oramikacin (15 mg/kg 4 times a day) can be given in combination with other antibiotics. In very severe situations ertapenem (4x1 g), imipenem/cilastatin (3x0,5/0,5 g), meropenem (3x1 g), or doripenem (3x0,5 g) can be administered. Preferred combinations: fluorokinolon + aminoglycoside, cephalosporin+ aminoglycoside, beta-lactamase stable penicillin+ aminoglycoside. Aminoglycosides administered once daily, for short term treatment, are less toxic.

Nitrofurantoin, norfloxacin, and first generation cepahlosporins have low concentration in tissues, so the use of these drugs is not advised. After 2 or 3 days of parenteral treatment, oral administrations of antibiotics can be continued, if the patient has no fever, and only mild symptoms.

In high risk, uncomplicated cystitis in adults, and with complicated UTIs, the therapy is the same as that described in acute pyelonephritis. In false negative pyuria doxyclineor macrolides are preferred.

The doses of drugs listed above are correct for patients with average body weight and preserved kidney function. In patients with a deteriorated function the lowering of the dose of

the selected antibiotics maybe necessary. The nephro-/ototoxicity of the given drug is an important issue.

In pregnancy, not only the cystitis itself, but even the asymptomatic bacteriuria must be treated. Preferred antibiotics: nitrofurantoin (2x100 mg, for 3-5 days), amoxicillin (3x500 mg, for 3-5 days), amoxicillin/clavulanic acid (2-3x625 mg, for 3-5 days), cephalexin (3x500 mg, for 3-5 days), fosfomycin (1x3 g one time). In pyelonephritis: ceftriaxone (1x1-2 g), aztreonam (2-3x1g), piperacillin-tazobactam (4x3,375-4,5 g), cefepim (2x1g), imipenem-cilastatin (4x500 mg), ampicillin (4x2 g), gentamycin (3-5 mg/kg/dayin 3 equal doses).

In uncomplicated, complication-free UTIs no control microbiological examination is necessary in establishingthe effectiveness of the treatment. In any other cases it is advised 2-3 days afterthe termination of the antibiotic treatment.

Other infectious diseases of the urinary tract

Special infections caused by species of **<u>Chlamydia and Mycoplasma</u>** are not part of internal medicine, but because of their relatively high frequency we must consider these infections, especially when there are bacteria and white blood cells in the urine sediment but the usual microbiological examination is negative (see false negative pyuria) and the patient has recurrent dysuria. The same is true for infections caused by Mycobacteria.

Infections caused by fungi come together with tumours, immunosuppressive treatments, catheters, diabetes mellitus and long term antibiotic treatment.

Prostate diseases

Diseases of the prostate belong to urology. Abnormal findings in the prostateduring rectal digital examination indicate thatan urological examination is necessary. Infections of the prostate also indicate urological examination. Fluorokinolones are preferred in these situations. Microbiological examination of the urine is mandatory.

The infection of the prostate has a diverse clinical picture:

- acute prostatitis
- chronic prostatitis
- Abacterial prostatitis (morefrequent than acute or chronic prostatitis, but the clinical symptoms are almost the same. The result of the microbiological examination is usually negative, despite pyuria. Because of the possibility of

Chlamydia or Mycoplasma infection, administration of macrolide antibiotics is preferred overtwo weeks).

Chapter 15.
Hereditary kidney diseases
Dr. Tibor Kovács

Chronic renal replacement therapy is required in approximately 10% of patients with end-stage renal failure due to various hereditary kidney diseases. Kidney cystic diseases mainly develop as a consequence of genetic mutations; however, numerous other but rare genetic diseases affecting the glomeruli and tubules are also known. In this following section we tend to discuss only the most important disorders.

Table: Hereditary kidney diseases

1. **Cystic disorders**
    a. Autosomal dominant polycystic kidney disease (ADPKD)
    b. Autosomal recessive polycystic kidney disease (ARPKD)
    c. Medullary sponge kidney (autosomal dominant)
    d. Juvenile nephronophtisis (autosomal recessive)

2. **Glomerular disorders**
    a. Congenital nephrotic syndrome
    b. Alport syndrome
    c. Thin basement membrane nephropathy
    d. Fabry disease (Anderson-Fabry disease)

3. **Tubular disorders**
    a. Gitelman syndrome
    b. Bartter syndrome
    c. Renal tubular acidosis
    d. PHA1, Gordon, Liddle syndrome
    e. Nephrogenic diabetes insipidus

4. **Inherited kidney tumors**
    a. Wilms tumor
    b. Von-Hippel-Lindau disease, Tuberous sclerosis complex 1, 2

Adult polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by multiple cyst formation affecting both kidneys bilaterally and may co-exist with cyst formation of other organs (e.g. liver, pancreas).

Pathogenesis

Several gene mutations could be attributed to the development of ADPKD. The PKD1 gene (chromosome 16) mutation occurs most commonly in 85-90% of cases, while PKD2 gene (chromosome 4) mutation could be detected at a lower rate. Moreover, families have been identified where neither the PKD1 or PKD2 mutation could be observed (PKD3?). In the majority of cases (95%) the disease is already acknowledged in one or the other parent; however, in 5% of cases it may also manifest via 'de novo' mutations.

The fact that renal cysts are being formed at specific parts of the tubules and that there are small numbers (<10%) of nephrons involved suggests that PKD mutation alone, which occurs in every cell, is not sufficient for cyst generation, thus additional mutation of these mutant cells is required for the total loss of the intact PKD allele (i.e. second hit theory) leading to overt cyst formation.

It is suggested that in this process tubules in affected cells first dilate, and that this is followed by gradual collations which then become the cysts covered with an epithelial cell layer. Subsequent enlargement of the cysts occurs owing to the fluid secretion into the lumen leading to mechanical compression of the surrounding intact tissue, consequently leading to the development of kidney failure.

Epidemiology

ADPKD is the third most common hereditary disease after hypercholesterolemia and otosclerosis, with which we are already familiar. The prevalence of genetically affected individuals ranges between 1:400 and 1:1000. The incidence shows no differences between the genders. In some populations the prevalence may be higher. There is a bimodal occurrence of the disease, showing a lower number of cases in childhood and the highest number of cases within the 30-50 year age range. In large numbers of cases the familial accumulation is clearly evident; however, there is a 5% incidence of sporadic cases ('de novo' mutation).

Diagnosis

Based on positive family history and findings from the abdominal ultrasonography (US) (i.e. at least 3-5 cysts in each kidney) it is easy to set up a diagnosis, which can often be confirmed through physical examination of palpably enlarged kidneys in the abdomen. Conversely, it is more difficult to make the diagnosis in young (as yet) asymptomatic patients or in cases with a negative family history. Regular follow-ups with abdominal US and genetic

testing may be useful. The disease could be excluded if the cysts do not develop by the age of 40 years. The lack of cysts at a younger age does not have a negative predictive value; it is therefore necessary to carry out follow-up imaging examinations of the patient.

Clinical manifestation

Apart from renal alterations (bilateral enlarged and cystic kidneys), other extrarenal manifestations (e.g. liver, heart, intracranial aneurysms) are often present in ADPKD. Enlarged kidneys that could be observed in all cases may be associated with dull abdominal discomfort and pain. Enlarged kidneys encompassing the abdominal cavity could cause digestive problems or compression of the inferior vena cava. The complication of cyst hemorrhage accompanied by massive (non-glomerular type) hematuria occurs relatively often (~40%) in ADPKD patients. The presence of macrohematuria, which could imply cyst hemorrhage, kidney stones, urinary infection as well as tumor, may cause differential diagnostic problems.

In ADPKD, **urinary tract infections (UTIs) and kidney stones** are more common than in the average population, likely as a result of obstruction of the urine flow caused by the cysts. UTIs are more frequent in female patients. Recurrent UTIs are common complications, is contributed the insufficient penetration of antibiotics into the cysts; hence, complete eradication of the infection is not usually feasible. More than half of all renal stones are composed of uric acid.

High blood pressure precedes the development of renal failure in three-quarters of patients, and hypertension is often the reason which makes the patient first turn to the doctor. Enlargement of the renal size concomitantly increases the blood pressure in the course of time. In the background, in response to reduced renal blood flow, increased angiotensin secretion and sodium retention may play a part. For this reason, the first choice of treatment should be salt intake restriction and administration of RAAS inhibitors. More than 90% of patients are already suffering from hypertension at the time of the development of uremia. In polycystic kidney disease, similarly to other chronic kidney diseases, hypertension accelerates the progression of decline in the renal function.

Liver cysts, which are described by abdominal US in more than 80% of patients, could be observed in the absence of any particular symptoms; however, mild tension of the liver area may be present. Interventions of liver cyst puncture may only be necessary in cases of severe complaints.

In ADPKD, there are two types of cardiovascular lesions that develop more frequently, although the pathophysiological mechanisms are unclear. One of them is **mitral heart valve prolapse,** which develops in approx. 25% of patients. The other is **intracranial aneurysm**, a possibly life-threatening lesion which develops in approx. 8% of patients and could be observed at any phase of the disease. The rupture of these intracranial aneurysms, caused by a sudden rise in blood pressure, leads to subarachnoid hemorrhage, often with fatal outcome. We therefore have to assume the possibility of intracranial aneurysms or their rupture in ADPKD patients exerting neurological symptoms and signs. In patients with a positive family history there is a threefold higher risk that such aneurysms will develop, which is why some recommendations suggest conducting cranial angio CT or MRI scans periodically (in every 3-5 years) in these families.

Pancreas and arachnoid cysts could be detected in 8-9% of cases, but these usually do not require any specific treatment or cause complaint to the patients.

As a consequence of enlarged kidneys, increased intra-abdominal pressure predisposes the oncome of **abdominal hernia (inguinal, umbilical)** formation, which could be observed in more than 10% of patients.

Therapy

The main treatment goal is to delay the progression of the kidney disease. Optimal blood pressure control plays the key role. RAAS inhibitors should be the first choice of antihypertensive drugs in treating high blood pressure.

In UTIs treatment, targeted and long-term antibiotic therapy is recommended. The lipophilic antibiotics possess a higher capacity to penetrate into the cysts. Based on clinical experiences, trimethoprim / sulfamethoxazole and fluoroquinolone types of antibiotics are primarily recommended to be used.

Symptomatic treatments should be applied in cases of pain and cyst hemorrhage. Sustained compressing symptoms may require interventions, such as cyst puncture or nephrectomy.

Our better understanding of cyst formation and growth has provided and led to testing several novel experimental therapies which, however, have not yet been introduced into the routine clinical settings. There have been studies with promising candidate drugs of cell proliferation inhibitors (mTOR inhibitors, and epidermal growth factor receptor tyrosine kinase inhibitors) and transepithelial fluid secretion inhibitors (vasopressin receptor 2 antagonist, somatostatin).

The most effective treatment may be kidney transplantation at the stage of end-stage renal failure; although removal of either or both enlarged polycystic kidneys could be necessary, causing disproportion. Enlarged kidneys might also contraindicate peritoneal dialysis.

Prognosis/Outcome

By the age of 60 years, 50% of patients with polycystic kidney disease require regular chronic renal replacement therapy. Poorer prognosis is evident, caused by certain factors including the onset of the disease before the age of 30 years, development of hypertension before the age of 35 years, race (there is a prevalence among blacks), or major macrohematuria.

Genetic factors also have impacts on the prognosis. The **prognosis is poorer in PKD1** than in PKD2, the latter showing more sustained and ulterior cyst formation, meaning that the development of renal insufficiency occurs earlier, at an average of 15 years in PKD1 as opposed to PKD2. The type of mutation may also affect the progression.

As one of the non-genetic factors, **uncontrolled hypertension** clearly worsens the prognosis. The roles of protein-enriched diet and smoking though are still ambiguous. Some reports highlight the role of **frequent recurring urinary tract infections** (cyst infections), which may also account for poorer prognosis.

Progression is more rapid in male patients.

It has not been possible to retain progression by performing cyst punctures which rather cause parenchyma injury upon the intervention.

Cyst growth and accompanying increases in the kidney size noticeably correlate with decline of the kidney function.

In patients with polycystic kidney disease, the renal anemia is usually not severe, or often does not develop compared with other chronic renal failure of different etiology, since the damage of tubules and peritubular cells is not progressive. In patients undergoing renal replacement therapy the rest diuresis could be preserved, remaining significant for longer periods than in other kidney diseases.

Autosomal recessive polycystic kidney disease (ARPKD)

ARPKD prevalence is 1:10,000- 1:40,000, hence it is less common than the ADPKD discussed above. It develops intrauterine. A large number of microcysts (< 3 mm) are formed as a result of PKHD1 gene mutation (chromosomal locus 6p12.2). Concomitant liver fibrosis

results in the development of portal hypertension. Where enlarged kidneys are present, the disease is diagnosed by US in the neonatal age. The perinatal mortality of neonates is fairly high (~30-50%).

Inherited glomerular disorders

Congenital nephrotic syndrome (CNS) or Congenital focal segmental glomerulosclerosis.

This hereditary disease shows autosomal recessive inheritance in which the proteins involved in the glomerular filtration process are altered.

The prevalence is lower than 1:10,000 live births.

There are several forms of the disease (e.g. Finnish type CNS) where mutations of genes encoding various proteins that are composing the slit membrane (e.g. nephrin, podocin, laminin) are affected most commonly.

The main feature of the disease is manifestation of nephrotic syndrome in the neonatal age or in infants, and subsequently the development of malnutrition and increased susceptibility to infections. It is worth noting that as they are genetic disorders the use of steroids and other immunosuppressive therapies is completely ineffective in these diseases.

Alport syndrome

The syndrome was named after Dr. Cecil A. Alport who first identified it in 1927. Alport syndrome, which is regarded as one type of hereditary nephritic disease, results from the mutations of the type IV collagen alpha subunit with the possible co-existence of sensorineural hearing loss and eye abnormalities.

The prevalence is 1:10,000-1:50,000.

Three gene-dependent separate manners of inheritance are known:

- X-linked dominant (80%)
- autosomal recessive (15%)
- autosomal dominant (5%)

Due to disturbed collagen synthesis the glomerular basal membrane (GBM) structure becomes abnormal.

The clinical picture appears diverse. In female patients the disease is moderate as there are fewer or no symptoms at all. In male patients the symptoms are more pronounced and deteriorate rapidly. The disease primarily affects boys and men. It may start with typical oligosymptomatic urinary abnormalities (glomerular hematuria) in boys aged 3-10 years followed by subsequent increases of proteinuria at later stages.

In several cases, the disease could be recognized only in young adulthood as severe therapy-resistant nephrotic syndrome (in 40% of cases, a poor prognostic sign) or rapidly progressive deterioration of the renal function.

The urinary abnormalities typically occur in conjunction with progressive bilateral sensorineural hearing loss within the high-frequency (2000-8000 Hz) range. Its recognition may be difficult as this range differs from the range of normal speech frequency. The loss of hearing worsens with the progression of renal failure, and advanced deafness develops in 50% of cases.

Urinary symptoms may initially include isolated hematuria (occasionally with macrohematuric episodes) followed by the gradual onset of progressive nephritic syndrome which might later turn into severe nephritic syndrome. Eye lesions develop in 30-40% of patients, mainly the anterior lenticonus.

Due to diverse renal manifestations (in the absence of familial history) diagnosis may be based on the findings of the electron microscopic examination of the kidney biopsy specimen, which can be confirmed by genetic testing. The kidney biopsy analysis is often not univocal, especially in the early stages. Differential diagnosis from thin basement membrane syndrome, IgA nephropathy and FSGS are often complicated.

Specific medical therapy is unknown. Treatments are symptomatic. Supportive care is difficult in cases of severe nephrotic syndrome. Both steroid and immunosuppressive therapy are inefficient in this disease.

It is a progressive disease; end-stage renal failure develops at the age of 15-35 years in male patients, whilst posteriorly in female patients.

Thin basement membrane nephropathy

Thin basement membrane nephropathy was previously termed as benign familial hematuria, since microscopic hematuria without progression into renal failure could be observed over several generations within families.

This autosomal dominant disease involves gene mutations of type IV collagen which, similarly to Alport syndrome, induces consistent thinning of the GBM (GBM thickness instead of normal 300-400 nm decreases to 150-225 nm).

Typically, the clinical picture is characterized by familial clustering of glomerular hematuria, and occasionally with macroscopic hematuric events. Microscopic hematuria can also be observed in 30-50% of family members. The prevalence shows no differences between the genders. Manifestations of other organs (eye, ear etc.) are not present in this

disease.

Histological examination provides differential diagnosis from IgA nephropathy. The diagnosis can be set up only by the electron microscopic examination of the kidney tissue section where the average thickness of the GBM is below 250 nm. The prognosis is good; therefore its differentiation from IgA nephropathy and Alport syndrome is important. It may be difficult to distinguish from early Alport syndrome, although the lack of extrarenal signs, proteinuria, hypertension, as well as progression in the loss of kidney function may be valuable.

Fabry disease (Anderson-Fabry disease)

Fabry disease, which involves genetic defects of the alpha-galactosidase enzyme leading to the intracellular accumulation of glycosphingolipids, affects the kidneys, the heart and the nervous system.

Analysis of the kidney biopsy sample may propose the diagnosis in patients presented with nephritic symptoms. It often progresses to end stage renal failure.

Specific treatment comprises lifelong enzyme replacement therapy with recombinant alpha-galactosidase enzyme.

Hereditary renal tubular diseases and kidney tumors are very rare conditions, their discussion exceeds the level of graduate nephrology education.

Chapter 16.
Acute kidney injury (acute renal failure)
Dr. Botond Csiky

Definition

Acute renal failure is an abrupt and usually reversible decline in the glomerular filtration rate, occurring over hours, days or weeks. This results in an elevation of serum blood urea nitrogen, creatinine, potassium and other metabolic waste products that are normally excreted by the kidneys. The term acute kidney injury (AKI), rather than acute renal failure, is increasingly used nowdays to refer to the acute loss of kidney function. This term also highlights that injury to the kidney that does not result is failure is also of great clinical importance. The term acute renal failure is now reserved for severe AKI, usually implying the need for renal replacement therapy.

AKI may be anything between a mild disease with transient decrease of renal function and/or urine volume or a life-threatening situation.

Epidemiology

AKI occurs in 3-7% of hospitalized patients. The cause is prerenal in 55-60%, renal in 35-40% and postrenal in <5% of cases.

Diagnosis

The signs and symptoms differ, depending upon the cause of the AKI.

AKI is generally detected by an increase in the serum creatinine and/or a decrease in urine output. A patient with AKI may be anuric, oliguric or non-oliguric.

In AKI the formulas for calculating GFR (eGFR) should not be used for assessment of renal function.

Prerenal AKI may be caused by **intravascular volume depletion** (extreme sweating, bleeding, vomiting, diarrhea, osmotic diuresis /e.g. in diabetic patients/, severe skin burning, hypertermia, pancreatitis, crush syndrome, hypoalbuminemia), **decreased cardiac output** (intrinsic heart diseases, pulmonary embolism, overdosing of antihypertensive medication, sepsis, liver failure), **constriction of renal arteries** (hypercalcemia, sepsis), **drugs causing impairment of the GFR autoregulation** (in renal artery stenosis angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and non-steroid anti-inflammatory drugs inhibiting the renal prostaglandin synthesis).

Renal causes: **diseases of the large kidney vessels** (thrombosis, embolism, large vessel vasculitis), **microvascular, glomerular inflammatory causes** (rapidly progressive glomerulonephritis, vasculitis, acute rejection), **microvascular, glomerular vasospastic causes** (malignant hypertension, toxemia), **microvascular, glomerular hematologic causes** (hemolitic uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation), **ischemic tubular injury** (caused by renal hypoperfusion), **tubular injury caused by toxin** (exogen toxins: antibiotics, antitumor sustances, X-ray, contrast media containing iodine; endogenous toxins: myoglobin, hemoglobin, immunoglobuline light chane, uric acid), **allergic interstitial nephritis**, **infections**, **acute rejection**, **tumorous infiltration**.

In postrenal cause there is obstruction in the **ureter**, **urinary bladder**, or in the **uretra.** The obstruction or its cause should be visualised using radiological methods. In some cases **extrauretral obstruction** may also be the cause in the form of a cervix or prostate tumor or (rarely) retroperitoneal fibrosis. In older male patients, prostate hypertrophy is a common postrenal cause of AKI. Classification of AKI is presented in the following **table**.

Table: Classification of AKI based on serum creatinine level, GFR decrease and urine output.

	Increase in serum creatinine of	GFR decrease	Urine output
Risk	>50%	>25%	<0,5 ml/bodyweight kg/hour for 6 hours
Injury	>100%	>50%	<0,5 ml/ bodyweight kg/hour for 12 hours
Failure	>200%	>75%	<0,3 ml/ bodyweight kg/hour for 24 hours, or anuria for 12 hours
Loss	Need for renal replacement therapy for >4 weeks		
End-stage renal failure	Need for renal replacement therapy for >3 months		

In order to establish the diagnosis of AKI, thorough history taking and physical examination, blood and urine analysis (mainly urinary sediment, specific gravity, urine sodium concentration), radiologic examinations (the most important is abdominal ultrasound examination to exclude the vascular and postrenal causes) and renal biopsy (typically in glomerular hematuria) are all required.

The clinical picture may indicate the cause of the AKI:

- if vomiting, diarrhea, bleeding, sepsis or decreased fluid intake is present in the history, the cause is likely to be prerenal.

- if tachycardia, sunken eyes, dry mucous membranes, decreased turgor of the skin, orthostatic hypotension are found on physical examination, the cause may be prerenal or acute tubular necrosis (the latter being the consequence of renal hypoperfusion)

- if the patient had bloody diarrhea and is olguric or anuric, hemolytic uremic syndrome may be the cause of AKI

- if the patient has macrohematuria and has had pharyngitis or impetigo a few weeks before the onset of macrohematuria, then postinfectious glomerulonephritis is likely

- if the patient has hemoptysis and AKI, then Goodpasture syndrome or Wegener's granulomatosis may be the cause

- purpura, petechia and joint pain together with AKI should raise the possibility of vasculitis (SLE, Henoch-Schönlein purpura)

- if AKI develops during hospitalization, acute tubular necrosis is the most common cause, developing as a consequence of hypotension, ischemia (sepsis or intraoperative hypotension) or a side-effect of nephrotoxic drugs (aminoglicoside, amfotericin-B, etc).

Treatment and prognosis

In prevention of the AKI, it is crucial to maintain an adequate blood volume and hydration state. In patients with malignancies, this is also important before and during chemotherapy. Nephrotoxic drugs should be avoided if possible; if not, than the serum concentration of these drugs should be monitored.

Treatment should be performed according to the etiology of AKI whenever possible. Volume, ion and acid-base homeostasis should be normalised. The manner and the time needed for the correction of these abnormalities differs according to the etiology.

In volume depletion iv. fluid substitution is needed, typically with cristalloid solution. In most cases physiological saline should be used. In renal failure the kidneys are not able to excrete potassium, so potassium containing solutions such as Ringer lactate should be avoided.

Hyperkalemia and metabolic acidosis are common; in these cases, conservative treatment of these abnormalities should be performed.

Hypervolemia may already be present at the time of diagnosis of AKI. It may also develop during the treatment of AKI, when fluid is supplemented in a higher amount than needed, as the fluid excretion capacity of the kidneys is also imapired. This may mostly occur in ICUs, where a large amount of parenteral fluid intake is needed for parenteral nutrition and medicine administration. In these cases iv. loop diuretics should be given. Furosemide is indicated only in patients with hypervolemia.

In AKI, treatment based on the etiology is very important. On the other hand, in AKI caused by iodine-containing radiologic contrast media, administration of 1200 mg N-acetylcisteine/day may be beneficial (although there are also studies on its inefficiency).

In patients with AKI, blockers of the renin-angiotensin-aldosterone system and non-steroid anti-inflammatory drugs should be avoided because these drugs reduce the renal blood flow. Most patients with AKI are in catabolic state, so dietary treatment is also important.

Renal replacement therapy does not shorten the time of recovery from AKI, but it is frequently needed for detoxication and volume regulation. There is no general rule on the time of the initiation or modality (intermittent or continuous) of renal replacement therapy. Renal replacement therapy is needed when severe hyperkalemia, hypervolemia (pulmonary edema),

metabolic acidosis and/or uremic symptoms (encephalitis, pericarditis, coagulopathy) are present.

Mannitol, bicarbonate, atrial natriuretic peptide, growth factors and insulin have been used in the treatment of AKI, with conflicting results.

Despite the fact that most patients with AKI do survive and have a grossly normal kidney function later on, in around 50% of patients subclinical renal damage can be detected after the AKI.

In 10% of the AKI patients irreversible or progressive kidney disease develops. These patients will need nephrological care later on.

Chapter 17.
Chronic kidney failure
Dr. Botond Csiky

Definition

Chronic kidney failure is a condition caused by diminished glomerular, tubular and endocrine kidney function affecting all the organ systems, characterized by high mortality rate and impaired quality of life. The signs of chronic kidney disease, like albuminuria, ≥ 30 mg/day or decreased kidney function (GFR < 60 ml/min/1.73m²) are present for at least 3 months, irrespective of the initial cause.

Epidemiology and stages

The most common causes (in order of prevalence): diabetic nephropathy > hypertensive nephropathy > glomerulonephritis > tubulointerstitial diseases > polycystic kidney > other causes.

The stages of chronic kidney disease (CKD) are presented in the table below.

Table: Classification of chronic kidney disease based upon glomerular filtration rate (GFR) and albuminuria

GFR stages	GFR (mL/min/1.73 m²)	Terms
1	>90	Normal or high
2	60 – 89	Mildly decreased
3a	45 -59	Mildly to moderately decreased
3b	30 - 44	Moderately to severely decreased
4	15 - 29	Severely decreased
5	<15	Kidney failure
Albuminuria stages	**Albuminuria (mg/day)**	**Terms**
A1	<30	Normal to mildly increased
A2	30 – 300	Moderately increased
A3	>300	Severely increased

Diagnosis

As a consequence of failing renal function, diverse signs and symptoms develop. The most prominent are due to the disturbance of the fluid and electrolyte homeostasis. The homeostasis of the intravascular volume and sodium are kept in a relative

balance as long as the GFR does not fall below 10-15 ml/min/1.73m². At this stage, symptomatic fluid- and sodium retention develops and progresses: hypertension, heart failure, peripheral- and lung edema may develop. Around 80-85% of end-stage renal disease patients are hypertensive. As potassium excretion is impaired, hyperkalemia is typical.

As a consequence of ion disturbances (mainly hyperkalemia), potentially life-threataning arrhythmias may develop.

Impairment of hydrogen ion excretion is also part of renal failure, causing metabolic acidosis to develop.

As the phosphate excretion and the synthesis of active vitamin D is impaired, hyperphosphatemia, secondary hyperparathyroidism, renal osteopathy and extraosseal (metastatic) calcification develop in soft tissues. Pain in the joints is also frequent. Progressive calcification of the arteries and the heart is a more severe consequence of the disturbance of the bone and mineralocorticoid homeostasis and is a major contributor to the high cardiovascular morbidity and mortality in this patient group.

Decreased erythropoetin synthesis and, less importantly, bleeding diathesis cause anemia, which is normocytic and normochromic if its only cause is erythropoietin defficiency. The diagnosis of renal anemia can only be established if other causes of anemia are excluded. Thrombocyte dysfunction is frequently present, aggravating the bleeding diathesis of uremic patients.

Gastrointestinal complaints (loss of appetite, nausea, vomiting, stomatitis, gastritis, gastrointestinal erosions, bleeding), serositis (pericarditis, pleuritis), erectile dysfunction, hypogonadism, infertility and amenorrhea may also be present.

As a consequence of central- and peripheral nervous system dysfunction, uremic encephalopathy (failing mental status, vertigo, coma), poly- and mononeuropathy, myopathy, muscle cramps and muscle weakness may develop. As a manifestation of sensorial neuropathy, burning feet or restless legs syndrome may also be present. In restless legs syndrome the legs of the patient when at rest move involuntarly. These syndromes have become less frequent in recent decades, probably because dialysis treatment has been initiated earlier than was earlier the case.

Most chronic kidney disease patients also have ischemic heart disease, cerebrovascular disease and peripheral arterial disease. Cardiovascular diseases represent the most frequent cause of morbidity and mortality in chronic kidney disease patients. Crural ulcus may develeop, based on several etiologies: ischemia, neuropathy, edema.

In uremia the immune system is supressed, so infections are common, representing the second most common cause of death in these patients. Malignant diseases are also more frequent than in the general population.

The skin of these patients is typically of a grayish-yellow colour. They frequently have pruritus and a typically unpleasant mouth smell (uremic fetor).

Laboratory abnormalities: high serum creatinine, blood urea nitrogen, potassium, phosphate, parathormone level and low calcium and albumin level, normocytic anemia in erythropoietin defficiency, microcytic anemia in iron defficiency, macrocytic anemia in folic acid defficiency, metabolic acidosis, elevated alcalic phosphatase enzyme level and on ultrasound examination small kidneys, eventually containing degenerative cysts. In oral glucose tolerance test insulin resistency can frequently be demonstrated (in 70-80%). Dyslipdemia (typically with high triglyceride and normal cholesterine level) is also frequent.

Treatment and prognosis

The aim of the treatment is to halt or slow down the progression of chronic kidney disease in order to improve the life expectancy and quality of these patients.

The most important therapeutic goals are the following:

- Abolish reversible causes of failing kidney function
- Control of fluid- and iron homeostasis
- Anemia therapy
- Treatment of bone-mineralocorticoid disorder
- Improvement of nutritional status
- Slowing down the progression of cardiovascular diseases
- Detoxication
- Treatment of infections
- Early diagnosis and treatment of malignant diseases.

Irrespective of the primary kidney disease, reversible causes may temporarily worsen the kidney function: decreased renal perfusion caused by hypovolemia (caused by vomiting, diarrhea, bleeding or excessive diuretic use), hypotension (caused by myocardial dysfunction or pericardial disease), infection (sepsis), drugs decreasing GFR (non-steroid antiinflammatory drugs or blockers of the RAAS). These causes should be eliminated as soon as possible.

In order to maintain adequate fluid balance, fluid intake should be restricted according to the amount of diuresis plus the amount of perspiration. A low sodium diet is important because in these patients the salt and fluid excretion is impaired, blood pressure is high and hypervolemia is present. Potassium excretion is also impaired, so a low potassium diet is also necessary. If the GFR has mildly to moderately decreased, a protein restricted diet is also advised. The daily protein intake should be 0.8-1.0 g/kg bodywieght/day. The aim of the low protein diet is to decrease the progression of the kidney disease. Implementing dietary therapy is important in order to prevent the development of a malnourished state as this reduces life expetancy. In patients on dialysis, a higher protein intake is recommended: > 1.2 g/kg bodyweight/day in hemodialysis and >1.3 g/kg bodywight/day in peritoneal dialysis because of the catabolic state and protein loss during the dialysis.

For the treatment of renal anemia erythropoetin or erythropoesis, a stimulating agent can be used administered parenterally (as they are polypeptides), if needed with iron and/or folic acid supplementation.

In secondary hyperparathyroidism, as a consequence of decreased phosphate excretion, decreased vitamin D synthesis and mineralisation defficiency, an elevated serum phosphate level is detected, which has to be decreased (by lowering the dietary phosphate intake, using phosphate binders, later on dialysis therapy); vitamin D supplementation is needed (with native or active vitamin D) or calcimimetics should be used (these modify the calcium sensitivity of the parathyroid glands). In some cases, when progressive extraosseal calcification, myopathy, therapy refracter severe uremic pruritus and tercier hyperparathyroidism are present, a parathyroidectomy is necessary.

Detoxication and the treatment of fluid- and ion disturbancies are presented in the next chapter. Here we only wish to mention that in ESRD diuretic treatment (in most cases furosemide) should be continued in order to maintain the patient's restdiuresis. Potassium binding resine can be used as part of the treatment of hyperkalemia.

As part of cardiovascular prevention, the patient should quit smoking, physical activity should be performed regularly, hypertension, dyslipidemia, disturbances of the bone and mineral metabolism should be treated, carbohydrate metabolism optimized and effective detoxication methods used.

When in ESRD patients the GFR falls below 30 ml/min/1.73m², the patients should be referred to a nephrologist (if the patients have not as yet been under a nephrologist's care). At this stage of the disease renal replacement therapy should be planned; options should be discussed with the patient and the patient should be prepared mentally and physically

(preparation of arteriovenous fistula or insertion of peritoneal dialysis catheter) for the renal replacement therapy. If the patient is suitable for kidney transplantation, and is also willing to eventually receive a transplanted kidney, the examinations needed for getting on the transplant waiting list should be started.

Chapter 18.
Renal biopsy

Dr. Gergő Attila Molnár

Diagnostics in nephrology usually starts by taking the case history, performing the physical examination, followed by general laboratory tests (electrolytes, blood urea nitrogen, serum creatinine levels, qualitative blood picture, erythrocyte sedimentation rate [ESR] urinalysis, routine imaging tests (renal ultrasound, Doppler) and more special tests (serology testing, special imaging analyzes) and renal biopsy. This is principally the last and invasive diagnostic method in nephrology (in non-urgent cases). We have to emphasize that the order of methods is not arbitrary, as also that in general, in the diagnosis of chronic internal diseases, we start with the most wide-ranging, least specific as well as least invasive methods (the case history, physical examination), and then upon information gained using these methods we move towards more specific and invasive tests, providing information on a more narrow field (e.g. CT, MRI, endoscopies). According to that, in the diagnostics of nephrological diseases, the need for the most invasive test, a renal biopsy, is indicated based upon results of less invasive tests. Just as in the case of general internal medicine an emergency (e.g. acute gastrointestinal bleeding) may overwrite the abovementioned order, similarly in nephrological cases, renal biopsy may move up the line of diagnostic tools, and in specific cases it has to be carried out urgently.

As is general for diagnostic tests, indications must be present, and contraindications should be absent. Indication in general means that the diagnosis required for the therapy cannot be established without renal biopsy.

Table: Indications of renal biopsy (more detailed)

- Acute kidney injury:
    - If it is not pre- or postrenal only
    - If acute tubular necrosis is not supposed to be in the background [a]
- Nephrotic syndrome or proteinuria > 2 gr/day
    - In adults always
    - In children: if the clinical picture suggests no minimal change syndrome to be in the background [b]
- Oligosymptomatic diseases:
    - Proteinuria: in cases of persistent (more than half year) > 1gr/day proteinuria [c]
    - Hematuria: persistent or recurrent hematuria of glomerular origin, especially in cases of concommitant proteinuria
- (Chronic) kidney disease of unknown etiology [d]

- Suspected renal manifestation of a systemic disease [c,e]
- Suspected inherited renal disease
- In cases of graft dysfunction after renal transplantation

[a]: If the clinical picture suggests acute tubular necrosis, but renal function does not start to improve after 2-3 weeks, the diagnosis should be revised and a renal biopsy must be carried out

[b]: In children, minimal change in the disease is found in the background of most cases of nephrotic syndrome. If the clinical picture corresponds to that, then initiation of therapy is reasonable even in the absence of renal biopsy, bearing in mind its potential complications. If the clinical picture does not correspond to minimal change or does not react to proper therapy, the biopsy has to be carried out.

[c]: Exception: e.g. clinically evident diabetic nephropathy may be in the background (persistent high HbA_{1c}, presence of diabetic retinopathy)

[d]: In the presence of activity signs (clinical activity signs, 'active' sediment, positive immunoserology etc.). Mainly in cases of suspected immunopathogenetic disease, for instance where it may aid in gauging the chance of recurrence in the transplanted kidney

e: E.g. in cases of suspected renal involvement caused by systemic lupus, multiple myelom, vasculitis

To judge contraindications and to prepare the patient for the biopsy, the following tests have to be undertaken: abdominal ultrasonography (kidney size, ruling out postrenal cause, renal cysts); blood coagulation tests: a qualitative blood picture (ruling out anemia, thrombocytopenia), prothrombin time, bleeding time and/or activated partial thromboplastin time; urinalysis; urine culture; blood pressure measurement; official blood group determination. The patient should be shifted from oral vitamin K antagonist to low molecular weight heparin, while platelet aggregation inhibitors (as well as NSAID) should be discontinued 5 days before the biopsy, if the cardiac status makes this possible.

The patient should be provided with detailed information, should make an informed decision after having been made beware of the potential complications, and should sign an informed consent sheet.

Table: Contraindications of renal biopsy in internal medicine:

- Absolute contraindications:
    - Predisposition to bleeding:
        - Platelet count < 100 G/L
        - Increase in PRT (> 1.2 x of reference value)
        - Increase in APTT (> 1.2 x of reference value)
        - Bleeding time > 10 minutes [a]
    - Expected lack of cooperation
    - Actual high blood pressure (> 160/95-110 mmHg)

- o Extensive renal cysts
- o Malignant kidney disease
- Relative contraindication:
  - o Small end-stage kidneys on imaging
  - o Anatomical or functional solitary kidney
  - o Actual pyelonephritis or abscess, urinary tract infection, febrile state (if it indicates infection)
  - o Anatomic alterations
  - o Obesity

[a]: May be corrected using desmopressine

The renal biopsy should be carried out using the rules of asepsis, if possible with real-time ultrasound guidance, by a doctor performing renal biopsies on a regular basis.

After the biopsy, a strict, 24 hour bed-rest, close observation (blood pressure, pulse rate, urine), and (except for patients with oliguric kidney disease) liberal fluid intake is required. New data suggest that frequency of biopsy complications may also be related to the type of renal disease, e.g. complications can develop with a higher chance in patients with suspected vasculitis, RPGN, acute interstitial nephritis or thin basement syndrome. The most frequent complications are bleeding: intra-, peri- or pararenal hematoma and arteriovenous shunts. Complications usually develop in the first 24 hours, for the diagnosis, routine blood picture analysis and ultrasound test (Doppler, as well) should be carried out the following day, even in a patient without symptoms.

The histological workup of the renal biopsy specimen should start as soon as possible: the pathologist divides the bioptate under a stereomicroscope into three parts for: 1) direct immunofluorescence, 2) light microscopic and 3) elektronmicroscopic analysis. In an ideal case, the result of the immunofluorescence analysis may be available on the day of the biopsy.

Chapter 19.
# Renal replacement therapy
Dr. Botond Csiky

Renal replacement therapies are: hemodialysis, peritoneal dialysis and kidney transplantation. Hemodialysis is used in most patients, but kidney transplantation is the most effective, the most physiological and provides the best quality of life. Worldwide, 89% of dialysed patients are treated with hemodialysis, 11% with peritoneal dialysis.

Hemodialysis

In hemodialysis the solute transport occurs through a semipermeable membrane with a large surface by selective diffusion, e.g. dialysis, where the blood and the dialysis fluid are on opposite sides of the membrane. According to the pore size of the membrane, small and middle molecularweight substances (up to 15.000 Dalton) can pass through the membrane.

In classical hemodialysis the solute transport occurs by diffusion, according to the concentration gradient between the dialysis fluid on one side of the mebrane and the blood on the other. In current dialysers the semipermeable membrane is present in the form of capillaries ("capillary dialyser"). The blood flows inside the capillaries and the dialysis fluid outside the capillaries, but within the housing of the dialyser in the opposite direction. The countercurrent flow increases the efficacy of the solute transport. By positioning the semipermeable membrane as capillaries, the surface of the membrane used for dialysis can be increased, which also enhances its efficacy. In the newer method of hemodiafiltration, a modern synthetic membrane is used with a larger pore size, where toxin- and considerable fluid removal is performed by diffusion and convection. By convection larger (middle molecularweight) substances can be eliminated with increased efficacy. Excess fluid is removed by ultrafiltration. In hemodialfiltration a considerable amount of the eliminated fluid (ultrafiltrate) has to be supplemented with what is known as substitution fluid. Dialysis is a life- preserving method in patients with ESRD

Figure: The dialyser
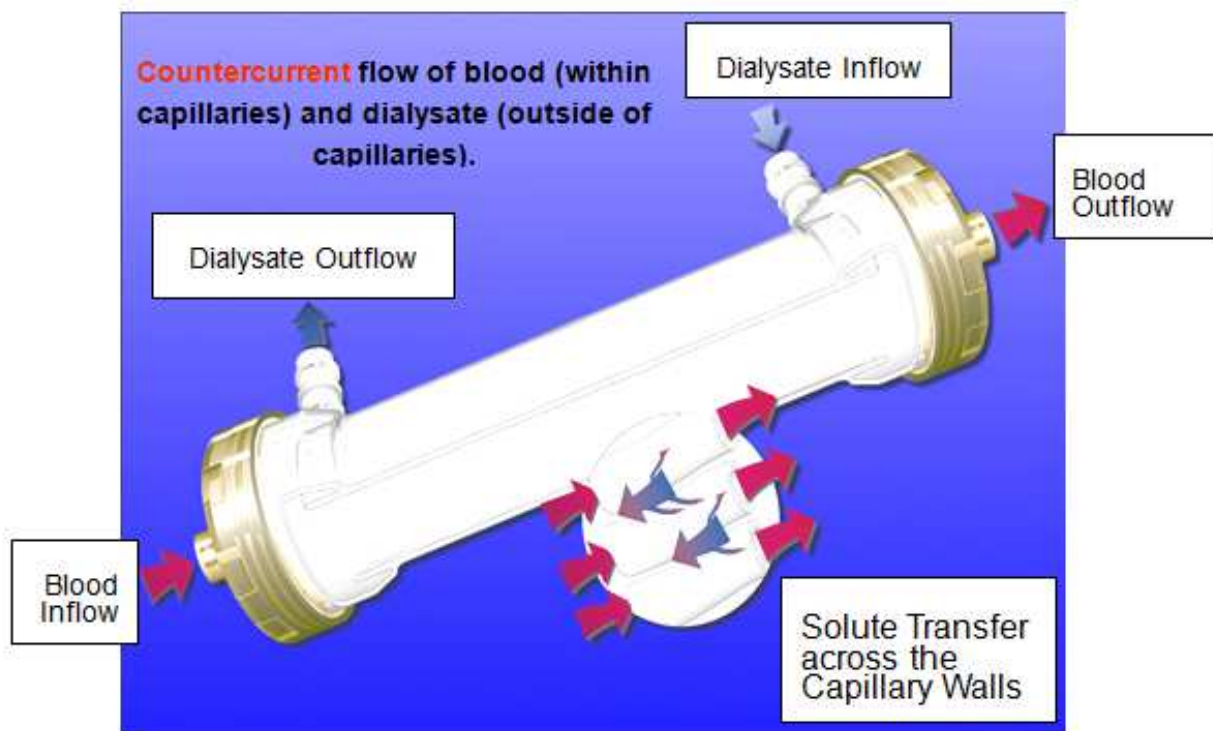
This method cannot detoxicate the kidneys because it is unable to eliminate large molecularweight toxins or protein-bound toxins. On the other hand, dialysis is an intermittent detoxication method (generally performed 3x4 hours weekly) compared to the continuous operation of the kidneys. Dialysis, in its imperfect way, can only replace the kidneys' excretory function. During treatment activation of the complement or kallikrein-kinin system or eventually of the white blood cells may occur.

As the blood exits the blood vessels and enters contact with artificial surfaces (needle, blood lines, dialyser) the coagulation system is also activated, so an appropriate anticoagulant has to be used. In most cases heparin is used for this purpose.

Figure: Schematic presentation of hemodialysis
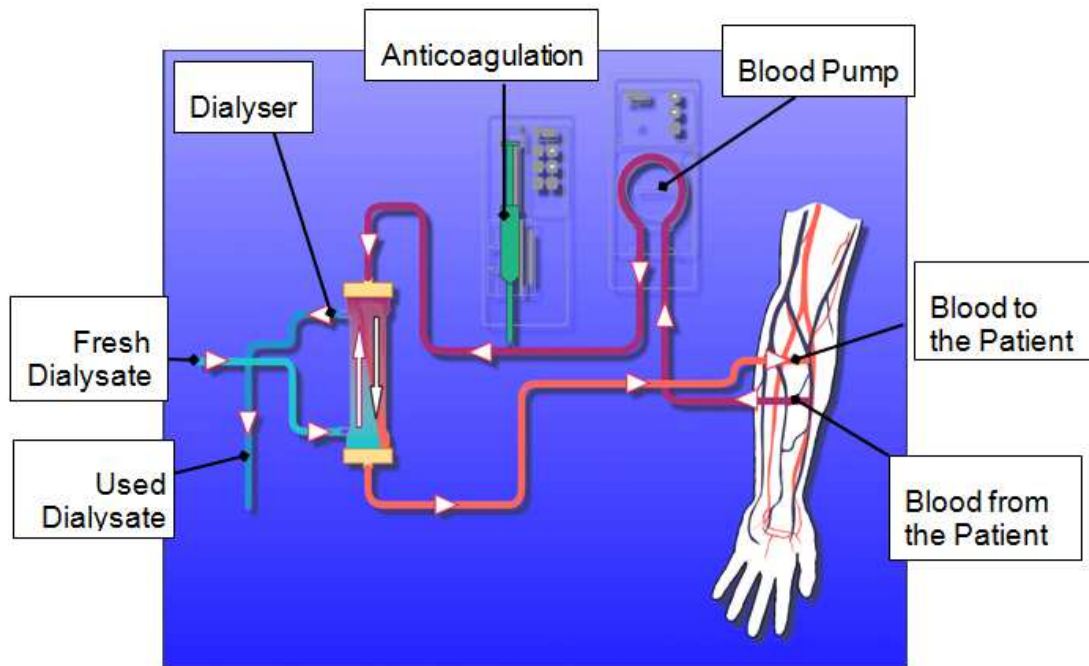
Adequate vascular access is required for hemodialysis, as a blood flow of 200-400 ml/min is needed for the treatment. For chronic hemodialysis the best vascular access is an arteriovenous anastomosis prepared on the non-dominant lower arm, typically in the tabatier fossa (Cimino's fistula). The anastomosis can be operated using a local anesthesia. In 6 weeks the fistula dilates make adequately possible the regular punction of the dilated vessel part with 2 needles in order to perform hemodialysis treatment. If it is not possible to prepare adequate anastomosis (due to vascular disease or after having several fistulas in many years of dialysis), the interponation of a synthetic vascular graft may be a solution. Another possibility is the insertion of a double-lumen catheter in the internal jugular, subclavian or femoral vein. For chronic hemodialysis, durable tunelled double-lumen catheters are available, inserted preferentially in the internal jugular vein.

For the purpose of chronic hemodialysis the ideal vascular access is the native arteriovenous fistula: it has the lowest complication rate, the highest efficacy and can be used for the longest time.

Absolute indications of initiating hemodialysis treatment: hyperkalemia which cannot be treated adequately in conservative way, pulmonary edema, uremic pericarditis or encephalopathy, hypertension (despite adequate antihypertensive treatment), bleeding caused by uremia, anorexia, nausea, vomiting. In patient under nephrological care, in the lack of uremic signs or symptoms, dialysis should be initiated when the GFR falls to or blow 8-10

ml/min. In most cases, at a GFR of 10 ml/min, uremic signs and symptoms develop making necessary the initiation of dialysis therapy. There is no single absolute laboratory value that indicates the start of dialysis. This decision has to be made by the nephrologist, taking into consideration the patient's primary kidney disease, concomittant diseases and the dynamics of the progression of CKD. Preparation for the initiation of dialysis (psychical preparation, Cimino's fistule operation, waiting for the maturation of the fistula, etc.) has to be started earlier. If the patient has explicit uremic symptoms, dialysis has to be initiated earlier.

Chronic hemodialysis treatment is typically performed in dialysis centers, 3 times/week, each dialysis session lasting 4 hours plus preparation for the dialysis and travel time to/from the dialysis center. Chronic hemodialysis has a profound effect on the patients' course of life.
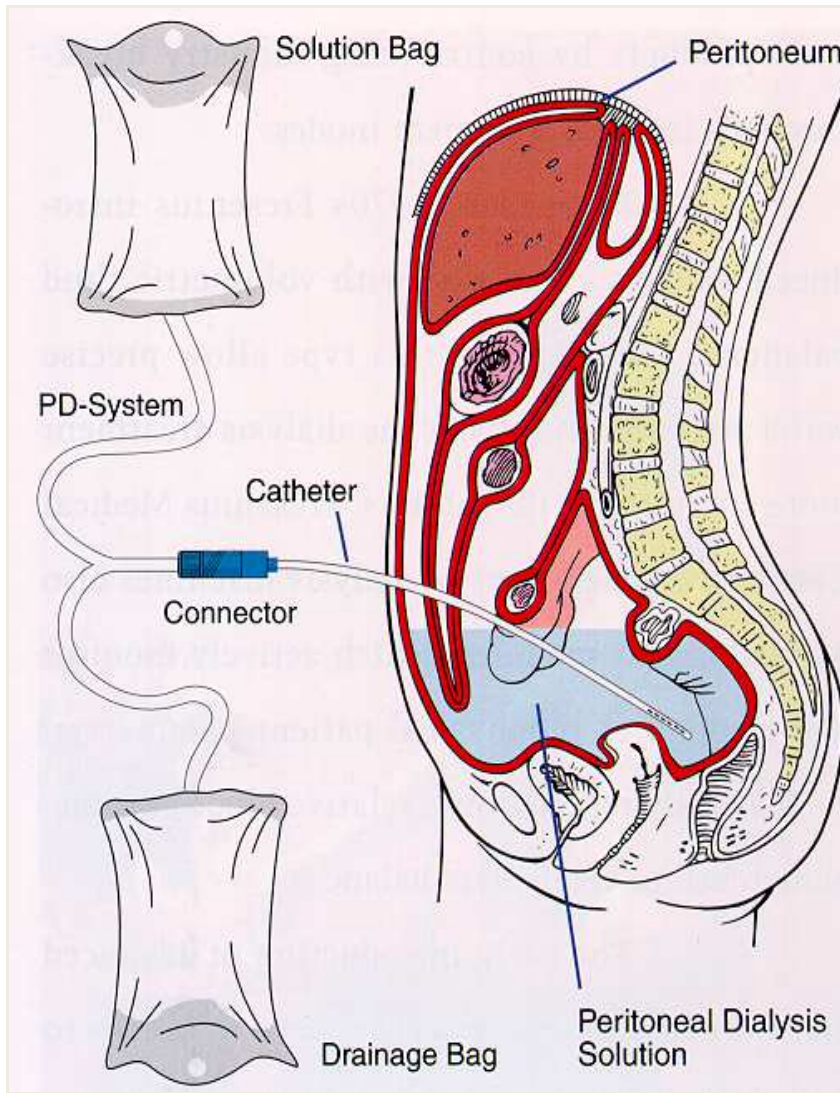

Peritoneal dialysis

In peritoneal dialysis the large surface of the peritoneal membrane is used for dialysis. A catheter (eg. Tecnkhoff's catheter) has to implanted surgically in the peritoneal cavity. The catheter is tunneled into the abdominal wall and its free end is outside of the abdominal wall. In continuous peritoneal dialysis (CAPD, the most common type of peritoneal dialysis) 2 liters of special peritoneal dialysis fluid is drained through the catheter in the peritoneal cavity, and it is exchanged 3-5 times/day, most commonly 4 times by the patient. The fluid exchange is performed with a single-use specific closed set in order to minimize the likelihood of getting bacteria (causing peritonitis) through the tubing system in the peritoneal cavity. In another type of peritoneal dialysis the fluid exchange is performed by a specific automated device (cycler), ideally in the patient's home, during the night, while the patient is sleeping.

Ultrafiltration (and by this volume removal) can be adjusted by modifying the osmotic activity of the peritoneal dialysis fluid. In most cases the osmotically active agent in the fluid is glucose, but it can also be amino-acid or glucose polymer (these are more expensive and less widespread). Glucose in the long-term is harmful to the peritoneal membrane. Some amount of glucose is always absorbed from the dialysis fluid, so it causes a permanent glucose load in the patient and by decreasing the glucose concentration of the peritoenal dialysis fluid, its osmotic activity will also be decreased (by this the ultrafiltration activity will also be diminished). Glucose is not the ideal osmotically active substance for the peritoneal dialysis fluid, so intensive research is being carried out to discover a similarly inexpensive

and effective agent to replace glucose in these fluids. Solute transport is performed via diffusion and convection.

Figure: Principles of peritoneal dialysis

The great advantage of peritoenal dialysis is that the patient is independent of the dialysis center compared to the hemodialysis (peritoneal dialysis patients routinely have to attend the dialysis center once monthly for examinations). It is a continuous detoxication method with continuous fluid removal (in hemodialysis these occur intermittently). No vascular access is needed (having vascular access may be problematic because of the severe atherosclerosis of ESRD patients). The treatment is performed by the patient (in special cases by someone, usually a relative, living with the patient) who has received specific training. The

patient is motivated as an active contributor to his/her treatment. Rehabilitation is easier and more effective for peritoneal dialysis patients than for hemodialysis patients.

The most significant complication of peritoneal dialysis is peritonitis. Compared with classical "surgical" peritonitis it has less severe symptoms. In most cases it is caused by bacteria. It should be treated with antibiotics given intraperitoneally. In most cases this is effective and sufficient treatment. If the peritonitis does not heal, relapses or the detoxication capacity of the peritoneal membrane is decreased after the peritonitis or serious adhesions develop in the peritoneum as a consequence of the peritonitis, the catheter has to be removed from the peritoneal cavity and hemodialysis has to be performed. In the rare cases of fungal peritonitis, the catheter has to be removed immediately and antimycotic treatment has to be started. It is impossible to perform peritoneal dialysis without the active contribution of the patient, in mentally retarded patients, or in patients physically incapable of performing peritoneal dialysis treatment, after multiple abdominal surgeries when adhesions of the bowels are suspected, and in patients suffering from inflammatory bowel disease or suffering from abdominal hernia.

There is no considerable difference in long-term patient survival between peritoneal dialysis and hemodialysis, but in the first 2 years of treatment the survival may be slightly better in peritoneal dialysis.

Since the intiation of chronic dialysis programs in the 60s dialysis patient survival has been improved considerably, mainly as a consequence of technical advances, but even today the 5-year survival rate is 30-50% in non-diabetic patients and around 25% in diabetic patients.

Transition between the methods of renal replacement therapy (hemodialysis, peritonealis dialysis and kidney transplantation) is possible in any direction, depending upon the patient's actual clinical condition and concomittant diseases.

Chapter 20.
Kidney transplantation
Dr. Tibor Kovács

Renal transplantation is the most effective therapeutic method in the treatment of end-stage renal failure, because for chronic uremic patients it *provides both better survival and quality of life* compared with other renal replacement modalities. The transplantation activity is determined by the number of available donor organs, of which necessitates are by far beyond of the accessible supplies in worldwide; hence there are different lengths of waiting lists over the separate countries.

According to US data, the total annual mortality of dialyzed patients is 16.1%, while it is 6.3% for those who are on the transplant waiting list, and it is only 2.8% in patients after transplantation with functioning kidneys (Wolfe 1999, Kaplan 2002). In patients aged at 18-39 years, the life expectancy depending on the renal replacement therapy is merely 15 years in those who are treated with chronic dialysis, whereas it gets up to 30-40 years (!) in those with transplanted kidneys. Among transplantations of different solid organs, transplantation of the kidneys is the most common exceeding the number of heart, lung, liver, etc. transplants.

Epidemiology

Annually, 250-400 kidney transplantations are carried out at the four medical university centers in Hungary (from cadavers: 251 and living donors: 40 in 2013; from cadavers: 340 and living donors: 48 in 2014, respectively). The first Simultaneous Pancreas Kidney transplantation in Hungary had been conducted at the University of Pécs, and since then such interventions are being performed by two transplant centers of Pécs and Budapest rating at 10-15 cases per year (14 cases in 2013; and 14 cases in 2014).

Regarding the rate of kidney transplantations expressed as number per one million subjects, the prevalence of kidney transplanted patients in Hungary is one of lowest among the European countries (i.e. 220 per million people). The transplantation activity is the greatest in Norway (i.e. 551 per million people). In addition to advances of the health care system, transplantation activity is highly influenced by the differences in social conventions, religions, and traditions. In Hungary, 11% of chronic dialyzed patients are getting enrolled in

the transplantation waiting lists perhaps due to the fact that proportions of dialyzed patients aged at > 65 years are continually increasing (approx. 57.4% in 2009).

From 2013 Hungary has been a fully comprehensive member of the Eurotransplant that involves several countries and helps to coordinate the optimal selection of the most suitable recipients. Consistently, the extended pool of organ donors provides transplantable kidneys more likely for those patients who are exerting rare genetic alleles or have been being on the waiting list for longer duration.

Appropriateness for transplantation

Patients with chronic renal failure exerting GFR < 20 mL/min are capable of being registered on the transplant waiting list (i.e. recipient candidates). Further conditions may include:

1. The patient's life expectancy after kidney transplantation has to be significantly higher than with any of the other treatment options.
2. The patient cannot be subjected to high risk by the surgical procedure (intermediate severity operation).
3. The patient's compliance has to be appropriate for sustained immunosuppressive therapy and infection-control afterwards.

Ad1. The limitation of age in recipient candidates for being registered is < 70 years. Other conditions that reduce life expectancy should be excluded (e.g. tumor, generalized vascular disease etc).

Ad2. The patient's cardio-pulmonary status has to allow the burden of the surgery. BMI should be < 35 kg/m2.

Ad3. The patient should not be suffering from any active psychiatric illnesses, and be compliant for accurately taking for long-term the prescribed immunosuppressive drugs.

In patients that seem suitable for transplantation, well-described and protocol-based diagnostic tests and examinations should be carried out, including blood- and HLA-typing analyses, complete medical, urological, gynecological, and dermatological examinations.

In case of pre-existing malignancy the transplantation may be performed following a waiting period for 2-5 years in average. HIV infection absolutely contraindicates the transplantation.

In patients with chronic renal failure due to type 1 diabetes mellitus, one therapeutic option may be the Simultaneous Pancreas Kidney (SPK) transplantation by which not only the dialysis treatment, but the exogenous insulin administration could be also terminated. In some countries, but unfortunately not in Hungary yet, pancreas transplantation following the kidney

transplantation could be also performed (pancreas after kidney; PAK) in patients with functioning kidney-graft (mostly in living donor kidney transplants).

Recipients showing the most compatible immunology with the cadaver donor are selected from the waiting list via an algorithm. The most suitable patients are searched by means of computerized registry system considering the HLA identicalness, antibody titers and other factors (e.g. children). This algorithm takes into account other aspects than the HLA antigens as well.

Living donor transplantation

Beside deceased donor organs, the kidney transplants may also be originating from living donors. The regulatory conditions of the living donor transplantation may vary in different countries. According to Hungarian regulations living donors may be family members, either close, own relatives or the spouses. The survival rate of living donor kidney transplants is markedly better compared to the cadaver donor transplants due to numerous factors, of which the most important are:

1. The recipient may be prepared with improved manners for the elective surgery;

2. The immunosuppressive therapy may be started by 1-2 days prior to surgery;

3. The so-called, cold ischemic time (i.e. time-lapse between excision of the kidney and blood supply with chilling, and restoration of the blood supply with re-warming) is notably shortened (1/2-1 hours of living versus 20-24 hours of deceased transplants).

The removal of kidneys from donors

The removal of kidneys from brain-dead or living donors is regulated by exceptionally strict laws. Interestingly, the number of brain-dead donors was shown to increase with the extensive use of big motorcycles, while it clearly decreased with intensified traffic safety regulations (airbags, speed limit, etc.). The transplantation activity of living donors in Hungary remained low compared to other similarly developed countries. It is noteworthy that donation of the kidney from living individuals are not associated with decreases in the quality or the life expectancy, whereas it considerably improves the recipient's survival and life expectancy.

Treatment after kidney transplantation

Since complete histocompatibility could not be assured, transplant recipients have to be given immunosuppressive therapy for the rest of their lives. The following

immunosuppressive medications are applied: steroids, cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, sirolimus, everolimus, rituximab, and IL-2 antibodies.

By means of using current immunosuppressive treatments, it is not uncommon that kidney graft keeps well-functioning for 15-20 years. For the kidney grafts in patients transplanted before 1989 the 10-year survival was 50%, whilst recently it may transcend 80%.

Post-transplant complications

Both acute and chronic forms of rejection may lead to rejection of the kidney transplant or gradual loss of the graft function. The complications of acute rejection may include fever, decreased urine production, swelling and/or sensitivity of the kidney transplant. Modification of the immunosuppressive therapy may prevent this event.

The term of chronic rejection seems deceptive, as it may occur as a result of immunological processes but atherosclerosis leading to same consequences could be also involved. Typical alterations consist of progressive and slow decline of the renal function and gradual increases of the blood pressure. On the other hand, contributions of the immunosuppressive drugs to this process also have a role, as adverse effects of these medications increase the risk of diabetes mellitus, hypertension, and higher lipid levels.

Mostly, the underlying causes in the deterioration of renal function in transplanted patients could be only determined by kidney biopsy that include, but are not limited to, the following:

- Rejection induced by inadequate immunosuppressive therapy
- Nephrotoxicity induced by immunosuppressive agents
- Opportunistic viral infections associated with immunosuppressive therapy more frequently

In addition to various viral infections (e.g. CMV, BKV) and bacterial infections, as a consequence of the long-term immunosuppressive treatment these patients are more susceptible to the development of different malignancies (e.g. post-transplant lymphoproliferative diseases – PTLD, Kaposi's sarcoma).

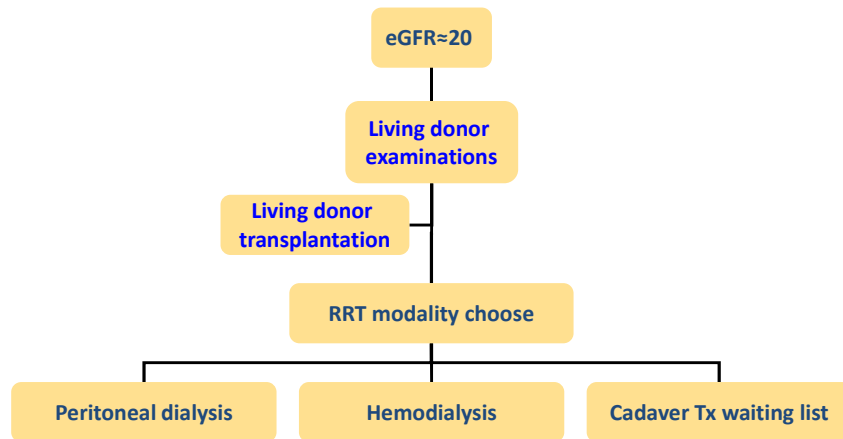**Re-occurrence of renal disease in the kidney transplant**

Re-manifestation of the primary kidney disease may occur at variable rates in the kidney transplant. For instance, in transplanted kidneys IgA nephropathy re-occurs in 50% within 2-5 years, the focal segmental glomerulosclerosis in approx. 10-30%, and the membranous nephropathy in approx. 3-30%. Typically, diabetic lesions in the kidney

transplant manifest earlier, within just a few years after transplantation; in contrast, diabetic nephropathy occurs usually after decades in the original kidneys.

Algorithm for choosing renal replacement therapy

Algorithm for choosing renal replacement therapy

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                           ┌─────────────┐
                           │  eGFR≈20    │
                           └──────┬──────┘
                                  │
                        ┌─────────┴─────────┐
                        │   Living donor    │
                        │   examinations    │
                        └─────────┬─────────┘
              ┌──────────────────┐│
              │  Living donor    ││
              │ transplantation  ││
              └──────────────────┘│
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                        │ RRT modality choose│
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  ┌────────┴────────┐    ┌────────┴────────┐    ┌────────┴────────┐
  │ Peritoneal      │    │  Hemodialysis   │    │ Cadaver Tx      │
  │ dialysis        │    │                 │    │ waiting list    │
  └─────────────────┘    └─────────────────┘    └─────────────────┘
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eGFR = estimated glomerular filtration rate (mL/min/1.73m^2)

Chapter 21.
Dosage reduction of medications adjusted to renal function
Dr. Richárd Halmai

General pharmacological considerations of drug administration in kidney failure and renal replacement therapy

Detoriation of the renal function alters the pharmacokinetics and pharmacodynamics of the drugs. For this reason, dosages of applied medicines should be adjusted accordingly. Patients with chronic kidneny disease are usually treated with combinations of several drugs, and so interactions are also important factors. Assessments of those drugs the serum or tissue levels of which can be measured are required in order to obtain the therapeutic dosages.

1) Pharmacokinetic aspects:

    a. Absorption

        i. Bioavailability – relative efficacy of drugs given non-intravenously compared to those given intravenously (iv)

            1. Edema of the gastrointestinal mucosa in renal failure may reduce the absorption of pharmaceuticals (e.g. furosemide), while the mucosa may also have the capacity to metabolize certain medicines

            2. In uremia, morning nausea and vomiting may reduce the absorption of medicines, and the contact time at which medicines are exposed to the gastrointestinal mucosa may also be reduced

            3. In severe uremia, the carbamide content of the saliva by changing the pH into the alcalitic range may also reduce the absorption of those medicines that have optimal absorption under acidic circumstances (e.g. ferrous – ferri conversion of iron is less effective leading to reduced bioavailability of the oral iron products)

            4. In severe renal insufficiency, metal containing phosphate chelators prescribed for reducing the hyperphosphatemia may also bind to other medicines, leading to their diminished absorption (e.g. thyroxine, fluoroquinolones, tetracycline, bisphosphonates)

            5. Heart failure, associated often with renal insufficiency, alters the absorption of drugs that are metaolized in the liver via "first pass

effect" (e.g. decreased first pass effect due to liver congestion increases the absorption of beta-blockers)

b. Distribution

    i. Distribution volume (distribution of drugs in the plasma and other compartments of the body) determines the initial dose of the given medicine (i.e. "loading dose")

        1. water-soluble medicines principally enter the plasma and the extracellular space, therefore their volume of distribution is relatively small

            a. edema, ascites and infections generally increase the distribution volume of water-soluble medicines, making it necessary to increase their loading dosage

            b. dehydration (e.g. emesis, diarrhoea, low fluid intake, hyperhdrosis, etc.), reduced muscle mass (e.g. uremic malnutrition due to the frequent nausea-emesis) decreases the distribution volume, thus it is recommended that the drug dosage is reduced

        2. lipo-soluble medicines distribute more equally in the body, resulting in a relatively large distribution volume, therefore the aforementioned factors have less impact on influencing the loading dose of these drugs.

    ii. Binding to plasma proteins

        1. The vast majority of different medicines bind to the plasma proteins. Un-bound fraction, also called free fraction, is responsible for affording the effects of drugs; and so changes of the plasma protein levels alter the effectiveness of drugs. It should be noted that while organic acids possess one binding site on the albumin, organic bases have in turn several binding sites on the glycoproteins.

        2. Due to hypoalbuminemia there are in nephrotic syndrome reductions in the plasma protein-bound fractions of drugs leading to increased free fractions of the drugs (e.g. furosemide, sulfonamide, warfarin, valproic acid). Decreased levels of the globulins lead to similar effects with the organic bases (e.g. digoxin). However, the

final therapeutic efficacy of drugs cannot be estimated consistently by these aspects alone, as it is influenced by numerous other factors. For instance, uremic toxins may antagonize medicines from the binding sites, increasing the availability of their free fractions for drug metabolism and elimination. In addition, due to significant albuminuria, larger proportions of the albumin-bound drugs are excreted via the urine (see also the ineffectivity of diuretics section). In chronic kidney disease, in response to acute and chronic subclinical inflammatory processes the serum level of alpha-1 glycoprotein increases, leading to an increased protein binding capacity in several drugs.

    c. Metabolism

        i. Upon metabolism the drugs are converted into more water-soluble forms in the liver required for subsequent excretion into the bile ducts or the urine via the kidneys. The drug metabolism (hepatic transformation) may be reduced in renal insufficiency. Importantly, one major aspect as to whether active (e.g. allopurinol-oxypurinol, cefotaxime-desacetylcefotaxime, tramadol-desmetyltramadol) or toxic (e.g. nitroprusside-tiocyanate) intermediate metabolites could be formed and whether these components are excreted via the kidneys should be considered to avoid the possibility of overdose or intoxication.

    d. Elimination

        i. The elimination of drugs and metabolites is undertaken predominantly through the kidneys, which is influenced by a number of factors, such as:

            1. renal blood flow

            2. glomerular filtration (depending on protein binding and the molecular size of drugs and the glomerular filter charge)

            3. tubular reabsorption and secretion (tubular secretion of drugs usually decreases with GFR - e.g. furosemide)

2) Pharmacodynamic aspects

    a. The history of medications should include previous intoxications, former and present effective treatments, the use of nephrotoxic drugs (e.g. aminoglycosides, NSAIDs, calcineurin inhibitors, etc.), which have to be reconsidered and if

necessary discontinued, and clinical/laboratory parameters (body weight, height and surface, hydration state, comorbidities – e.g. liver disease!).

b. A number of drug interactions may occur; for example, in transplant patients the administration of antifungal drugs, calcium-channel blockers, macrolid antibiotics, or grapefruit juice could lead to severe intoxication with calcineurin inhibitors by increasing absorption and/or decreasing the metabolism of the drug. In contrast, other drugs (e.g. carbamazepine, barbiturate, and rifampicine) could enhance the induction of enzymes (CYP3A4) that are responsible for drug metabolism, and by increasing the metabolism of calcineurin inhibitors could increase the risk of graft rejection.

c. In patients with chronic renal failure, the loading dose of drugs is equal to that used in patients with normal renal function and normal hydration status, whilst maintaining dosages should be adjusted to the declined renal function according to the glomerular filtration rate (GFR). The determination of GFR could be either estimated or assessed (see detailed discussion in another chapter). In chronic renal failure, the use of potassium-sparing drugs due to the increased risk of hyperkalemia (e.g. ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, potassium-sparing diuretics), and sodium intake due to the resultant hypertension (due to fluid accumulation as a consequence of increased salt sensitivity) should be managed with caution. In chronic renal failure, due to platelet dysfunction the risk of bleeding increases with the use of platelet aggregation inhibitors and oral anticoagulant threrapy. In chronic renal failure, only the active form of vitamin D is effective.

d. Achieving the optimal serum and/or tissue level of drugs may be completed by increasing the intervals between administrations and/or reducing the dosages, depending on whether appropriate peak serum level (e.g. aminoglycosides) or adequate stable serum level (e.g. penicillins) is required for the effect. When feasible, the serum level of drugs should be monitored (e.g. detection of Xa factor activity for low molecular weight heparines, digoxin, calcineurin inhibitors, carbamazepine, lithium, etc.), for this markedly increases the safety of the applied therapy.

e. After renal replacement therapy (hemodialysis, peritoneal dialysis) it is necessary to administer an additional dosage of drugs so as to substitute the active substance that was dialysed out during the treatment.

f. The use of some drugs is related specifically to kidney replacement therapy. For example, due to extracorporal blood flow intravenous heparine or low molecular weight heparine is given to prevent thrombosis upon hemodialysis. Here, antibiotics are given intraperitoneally through the Tenckhoff catheter to treat peritonitis as one of the complications of peritoneal dialysis.

3) In the clinical practice of medicine, dose adjustments of frequently used drug-groups require special concern. Of these, a few groups are discussed here in greater detail. Data on the applicability of commonly used generics are listed in **Table.**

a. Nonstreoid anti-inflammatory drugs (NSAIDs)

NSAIDs promote the further decrease of GFR by suppressing the renal production of prostaglandins in patients with chronic kidney disease. NSAIDs may cause sodium and consequent water retention, as well as hyperkalemia, even in the case of moderate renal impairment. Consequently, a thorough overview of indication and administration of NSAIDs is essential. The use of NSAIDs in patients with chronic renal failure and co-existing congestive heart failure, exsiccosis, or liver disease is contraindicated. In comparison of selective COX-2 inhibitors with non-selective COX-inhibitors there are no additional benefits provided, and the use of either group may result in such complications as acute interstitial nephritis and minimal change disease.

b. Analgetics

The majority of painkillers are metabolized and excreted via the liver and the biliary apparate; however, active metabolites may also be formed and accumulated, leading to central nervous system injury and seizures. Tramadol, as one of the mild opioids, is administered commonly, although it is often tolerated poorly due to the accumulation of active metabolites. Morphine should not be used in patients with renal failure; instead, hydromorphone could be administered for alleviating intense pain.

c. Antihypertensive and cardiovascular medications

In patients with renal failure, the dose of ACE inhibitors and angiotensin receptor blockers should be titrated gradually, monitoring the potassium level and the renal function. Regular ECG controls should be used in patients receiving antiarrhytmic drugs (foremost in checking QT interval and QRS width). Diuretics are often used in renal patients for treating

hypertension and hypervolemia, although the forceful use of diuretics may lead to hypovolemia and prerenal kidney failure. At GFR < 30 ml/min, the use of spironolactone, amilorid, and triamteren is contraindicated due to the higher risk of hyperkalemia. The tubular secretion of diuretics decreases parallel with renal impairment, making it impossible to attain the site of action. Consequently, in contrast to most of the drugs in renal failure, the dose of diuretics needs to be increased for their expected effect to materialise! Thiazide diuretics given alone at the creatinine-clearance < 30 ml/min act merely as antihypertensive drugs (and not as diuretics); however, in combination with loop diuretics they markedly potentiate the effects of loop diruetics due to what is known as the "sequential nephron blockade". By using the sequential nephron blockade prior to administration of the loop diuretics intravenously in bolus (20-40 mg), or constantly in severe cases (at the dose of 4-60 mg/hr after the bolus) and under the control of salt restricted diet (< 4 gr/day), patients receive 25-50 mg hypothiazide per os, which inhibits the sodium reabsorption in the distal convoluted tubuli that increased compensatory to the loop diuretics, thus enhancing the efficacy of loop diuretics. When therapy appears ineffective, combination with spironolactone (100-200 mg/day) or amilorid (5-10 mg/day) could be added in hospitalized patients under the tight control of serum electrolytes and the renal function, and avoiding severe ototoxicity.

The therapeutic options are more tapered in uremia, as the tubular secretion is competitively engaged between the uremic aninons, loop diuretics, NSAIDs, and certain antibiotics (e.g. penicillins). It is noteworthy that sustained use of loop diuretics at higher doses may lead to toxic tubuli injury.

Ultrafiltration may be necessary as a last refuge in life-threatening, therapy refractory edema. Here, fluid excess / edema is removed via a high-flow central vein canule during a hemodialysis session.

d. Anti-microbial drugs

It is very important for renal patients to receive the appropriate loading dose of the anti-microbial medications. This in most cases is equivalent to that used in patients whose kidneys function normally! The dose reduction

due to renal impairment should be taken into account only when the maintenance dose is calculated. An insufficient loading dose could lead to ineffectivity, whereas higher maintenance doses could lead to intoxication due to the accumulation of the drug or its active metabolites.

Dose adjustments may be completed either by giving reduced doses of the drug at normal intervals, or normal doses but after longer time periods. To avoid nephrotoxicity, it is preferred that aminoglycosides be administered once per day. Unfortunately, detection of their serum level is often unsatisfactory, since these antibiotics may lead to nephrotoxicity at normal serum levels, so observation of the clinical signs is essential.

Of the antiviral drugs, both the active substances and metabolites of acyclovir and gancyclovir can accumulate in renal failure, manifesting as neuropsychiatric symptoms. It should be noted that uremic symptoms might be masking the signs of the infection and overdose!

e. Anti-diabetics (with potential hypoglycemic activity)

Diabetic nephropathy is the most common cause of end stage renal disease; therefore the use and dosing of antidiabetics in renal patients have important roles. Kidneys are responsible for the insulin elimination. Therefore, as the renal function declines the clearance of insulin becomes reduced, which in the absence of any dose reduction could lead to hypoglycemia.

Among the sulfonylureas, gliquidon can be used, even in hemodialyzed patients. The use of incretin mimetics in renal failure requires suitable dose reductions.

f. Cytostatic drugs, biological therapy

   a. A number of cytostatic and biological therapies are widely used in kidney and other diseases. Regular measurements of the serum level of the given drug, as well as examinations of clinical signs at follow-ups, are critical in renal patients being treated with potentially nephrotoxic medications. The key goal is to help patients to recover whilst being attentive to the principle *nil nocere* by avoiding drug overdose and intoxication and by recognizing in time possible reversible adverse effects of the drug.

Table: The dose adjustments of frequently used pharmaceutical groups in the clinical practice of medicine; nephrotoxicity

Pharmaceutical group	Change of dose is NOT required	Change of dose is REQUIRED	Nephrotoxicity
H$_2$ receptor blockers	x		
Proton pump inhibitors	x		interstitial nephritis
HMG-CoA reductase inhibitors		x	rhabdomyolysis
Fibrates		x	rhabdomyolysis
Ezetimib	x		
Laxatives	x		prerenal acute kidney injury
Anti-diarrhoeals	x		
Anti-spasmodics		x	
Propulsive drugs		x	
Serotonin antagonists	x		
Folic acid analogues		x	tubulotoxicity
NSAIDs		x	acute renal failure; interstitial nephritis; nephrotic syndrome
Muscle relaxants		x	
Anti-gout medications		x	prerenal acute kidney injury
Bisphosphonates		x	acute kidney failure
Opioids		x	
Pharmaceutical group	Change the dosing is NOT required	Change the dosing is REQUIRED	Nephrotoxicity
Narcotics and sedatives		x	
Tetracycline	x		
ß-lactam penicilline derivatives		x	interstitial nephritis
ß-lactam cephalosporines		x	interstitial nephritis
ß-Laktam-carbapenems		x	interstitial nephritis
Sulfonamides and trimetoprim		x	interstitial nephritis; kidney stones
Macrolids		x	interstitial nephritis
Lincosamides		x	

Aminoglycosides		x	direct tubulotoxicity
Quinolone		x	interstitial nephritis
Glycopeptides		x	interstitial nephritis
Imidazole derivatives	x		
Nitrofuran derivatives		x	
Antimycotics		x	prerenal acute kidney injury, tubulotoxicity, reanl diabetes insipidus
Antiviral drugs		x	

Pharmaceutical group	Change of dose is NOT required	Change of dose is REQUIRED	Nephrotoxicity
Cardiac glycosides		x	
Antiarrhytmics		x	
Sympathomimetic drugs		x	
Nitrates	x		
Ivabradine		x	
Imidazolin receptor agonists		x	
Alfa-adrenerg receptor blockers	x		
Beta-blockers	x		
Calcium channel blockers	x		
ACE inhibitors		x	prerenal acute kidney injury
Angiotensin receptor blockers		x	prerenal acute kidney injury
Biguanides		x	
Sulfanylureas		x	
Alpha glucosidase inhibitors		x	
Thiazolidindiones		x	
Incretin mimetics		x	

Chapter 22.
Acid-Base Disorders
Dr. Judit Sebők

The pH, which is the negative logarithm of the H-ion concentration, is strictly regulated by the body homeostasis aiming to keep it between 7,35-7,45.

During the process of food metabolism volatilic acid (carbonic acid, then CO_2) and fixed acids (e.g. phosphoric acid, sulfuric acid etc.) are produced. At first these acids are neutralized by the buffering systems then the volatilic acid is eliminated by the lung, the fixed acids are excreted by the kidneys. Excessiv acid or base load, disturbances in the respiratory and renal system increase (acidosis) or decrease (alkalosis) the H-ion-concentration

Respiratory acid-base disturbances are consequences of primary respiratory disorders such as underexcretion or overexcretion of pCO_2. Metabolic acid-base disturbances arise as a result of either fixed acid accumulation or disorders of the renal bicarbonate reabsorption or production.

Primary respiratory disorders elicit metabolic responses, primary metabolic disorders invoke respiratory responses to compensate changes in pH.

Diagnostic approach to acid base disorders

The diagnosis is based on arterial or capillary blood gas analysis. Table shows the normal values of the most important measured and predicted parameters

Table: Normal values of the most important ABG parameters

Parameter	Normal value
pH	7.4 (7.35-7.45)
pO_2	80-100 mmHg
pCO_2	40 mmHg (35-45 mmHg)
Bicarbonate concentration	24 mmol/l (22-26 mmol/l)
BE (Base excess)	± 2.5 mmol/l

First we evaluate whether we have to do with acidemia (pH <7, 35) or alkalemia. (pH >7,35), then we find out that the overriding disturbance is metabolic or respiratory.

In case of metabolic disturbances the HCO_3^- concentration is changing primary and in a greater proportion. The way of change in pH, HCO_3^- and the compensatory pCO_2 change is

the same (metabolic acidosis: low pH, low HCO_3^- low compensatory pCO_2 / metabolic alkalosis: high pH, high HCO_3^- high compensatory pCO_2)

If respiratory disorder is present, the elementary difference is the pCO_2 -abnormality. The HCO_3^- is changing in the same way, but proportionally in smaller rate, pH is changing in different way (respiratory acidosis: high pCO_2 high compensatory HCO_3^- low pH and vice versa in respiratory alkalosis). (Figure 14 and Table 24.)

The degree of physiologic compensation can be predicted or calculated from relationships showed in Table 24. If the measured value (in ABG) correspond to the predicted values of compensation we have a simple form of acid-base disorder. If the predicted value differs from the measured one, we face with a mixed acid-base disorder (concurrent metabolic and respiratory disturbance)

Table: Acid-base disorders and prediction of compensatory responses

Disorder	pH	Primary change	Compensation	Comensatory Mechanism	Predicted value of Compensation
RESPIRATORY ACIDOSIS	↓	↑↑ pCO_2	↑ HCO_3^-	new HCO_3^- production in the kidney	10 mmHg pCO_2 ↑ → 1-4 mmol/l HCO_3^- ↑
RESPIRATORY ALKALOSIS	↑	↓↓ pCO_2	↓ HCO_3^-	↓ HCO_3^- reabsorbtion in the kidney	10 mmHg pCO_2 ↓→ 2-4 mmol/l HCO_3^- ↓
METABOLIC ACIDOSIS	↓	↓↓ HCO_3^-	↓ pCO_2	Hyperventillation (overexcretion of pCO_2)	1 mmol/l HCO_3^- ↓ → 1,1 mmHg pCO_2 ↓
METABOLIC ALKALOSIS	↑	↑↑ HCO_3^-	pCO_2↑	Hypoventillation (Underexcretion of pCO_2	1 mmol/l HCO_3^- ↑ → 0,7 mmHg pCO_2 ↑

pH

pH <7.35 | pH 7.35-7.45 | pH >7.45

Acidosis | Normal | Alkalosis

HCO_3^- ↓↓ Metabolic acidosis | pCO2 ↑↑ Respiratory acidosis | HCO_3^- ↑↑ Metabolic alkalosis | pCO_2 ↓↓ Respiratory alkalosis
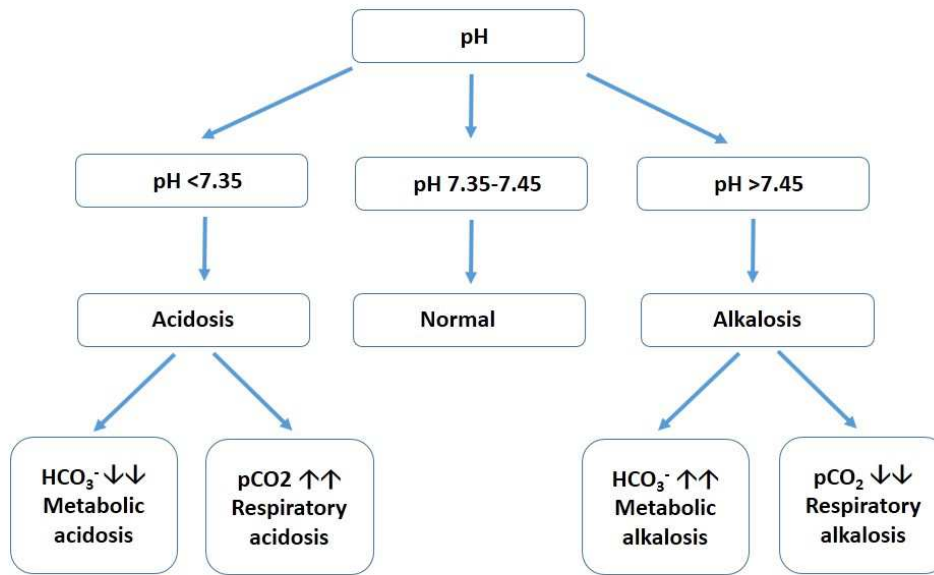
Figure: Evaluation of acid-base disorders

Calculating anion gap is the next step in the differential diagnosis of acid base disorders. It is an important diagnostic procedure in the evaluation of metabolic acidosis.

The anion gap equals the difference between the plasma concentrations of cations (the major cation, Na) and anions (chlorid and bicarbonate).

Anion gap$= Na^+ - (Cl^- + HCO_3^-) = 12 +/- 2$ mmol/l.

Raised anion gap (high anion gap) is usually due to the accumulation of non-measured anions (acids). In case of bicarbonate loss the low HCO_3^- concentration is compensated by the increase of Cl^- concentration, so the anion gap remains normal (normal anion gap metabolic acidosis)

Metabolic acid-base disorders
Metabolic acidosis.

Metabolic acidosis results from acid load or alkali loss. Acid load can occur due to overproduction or accumulation of endogenous acids (the latter is seen in severe renal failure) or accumulation of exogenous acids (intoxication). Metabolic acidosis due to acid accumulation goes with high anion gap. Alkali can be lost from the gastrointestinal tract or from the kidneys. In case of bicarbonate loss the anion gap remains normal. Table 25. shows the most common causes of metabolic acidosis

1) **High-anion gap (normochloremic) metabolic acidosis (acid load)**
   a) Ketoacidosis
      a. Diabetic ketoacidosis
      b. Alcoholic ketoacidosis
      c. Starvation
   b) Lactic acidosis (L lactat)
      a. Type A (Hypoxia)
      b. Type B (Absence of Hypoxia)
   c) Renal failure
   d) Ingested toxins (acids or agents which metabolise to acid)
      a. Ethylen-glykol
      b. Methanol
      c. Salicylates
2) **Non-anion gap (hyperchloremic)metabolic acidosis (alkali loss)**
   a) Extrarenal bicarbonate loss
      a. Diarrhea, Laxative abuse,
      b. Ureterosigmoidostomy, jejunal loop, ileal loop
   b) Renal bicarbonate loss
      a. Renal Tubular Acidosis

Table: Most common causes of metabolic acidosis.

High-anion gap (normochloremic) metabolic acidosis (Table)

The accumulation of ketoacids such as acetoacetat and beta- hydroxybutyrate accounts for the increment of anion gap in ketoacidosis. Lactic acidosis is a result of an imbalance between the production and / or use of lactic acid. Type A lactic acidosis characterized by acute hypoxia or tissue underperfusion e.g. in shock, sepsis, severe anemia or carbon monoxide poisoning. There is no tissue underperfusion or hypoxia in type B lactic acidosis, it occurs in hereditary disorders of glucose and lactate metabolism, in neoplastic diseases, in liver failure or as an effect of some drugs, like for example metformin.

In severe acute or chronic kidney disease when GFR falls under 15-20 ml/min accumulation of sulfates, phosphates and other organic anions leads to high anion gap acidosis (uremic acidosis)

Ingestion of ethylene glycol and methanol leads to metabolic acidosis due to the accumulation of their toxic metabolits. Both are metabolized by alcohol dehydrogenase and aldehid dehydrogenase resulting in glycolic acid and oxalic acid in etylen glycol-, and formic acid in methanol poisoning.

In salicylate (aspirin) intoxication the high anion gap metabolic acidosis is secondary to accumulation of salicylicacid.

Non-anion gap (hyperchloremic) metabolic acidosis (Table)

In chronic severe diarrhea bicarbonate is wasted by the stool. Surgical diversion of the ureter into an ileal- or jejunal pouch or into the sigma may be associated with the development of metabolic acidosis. The bicarbonate loss is caused either by the reabsorption of urinary NH_4Cl by the intestine or by the exchange of urinary Cl^- to bicarbonate in the gut.

Renal origins of bicarbonate loss are the different forms of renal tubular acidosis. RTA is a condition when the renal tubules are not able to acidify the urine appropriately.

Diagnostic approach

Figure shows the differential diagnosis of metabolic acidosis.

Figure: Differential diagnosis of metabolic acidosis
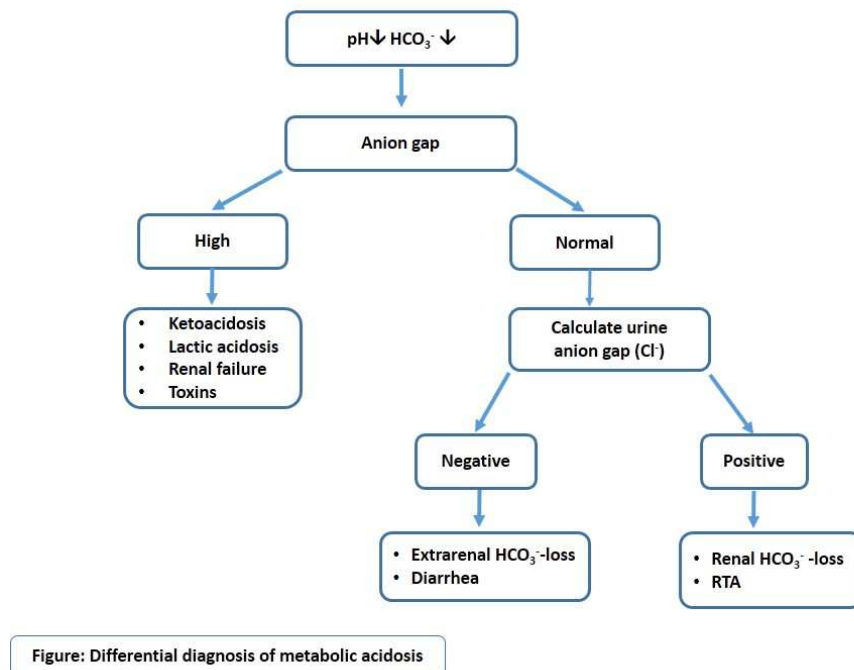
After metabolic acidosis is diagnosed, serum anion gap has to be calculated which is for differentiating between conditions of acid load or base loss.

In high anion gap acidosis a probe of the history, and examination of laboratory tests like blood glucose, lactate, renal function, blood alcohol level, and toxicology etc. will help in determination of the underlying cause.

Symptoms

In mild acidosis patients are usually asymptomatic, but headache, fatigue, abdominal pain, nausea or vomiting may occur.

Severe metabolic acidosis is typically accompanied by Kussmaul respiration, which is the characteristic sign of respiratory compensation. Tachycardia, arrhythmias, depressed myocardial contractility and decreased vascular and cardiac catecholamine sensitivity may be present. All of them predispose to hypotension and pulmonary edema. Central nervous system function is depressed leading to more serious disturbances of consciousness.

Role of metabolic acidosis in kidney disease.

Acidosis increases bone resorption thus aggraviating the deterioration of metabolic bone diseases accompanying CKD and tubular dysfunctions (RTA).

Chronic metabolic acidosis is independently associated with progressive loss of renal function.

Treatment

Detection and treatment of the underlying disease and etiological factors is elementary.

In diabetic ketoacidosis the primary treatment is aimed to intravenous fluid replacement followed by insulin and - as required - glucose administration. Therapy of alcoholic ketoacidosis should focus on glucose and fluid supplementation. The underlying condition that disrupts lactate metabolism (e.g. hypoxia, tissue hypoperfusion) must be corrected in the first-line treatment of lactic acidosis.

Etylene-glycol and methanol intoxication is treated by ethyl-alcohol or fomepizole which inhibit function of alcohol dehydrogenase so as to prevent formation of toxic metabolites. Hemodialysis is required to remove parent compound and its metabolites.

Alkaline urine pH leads to increased urinary excretion of salicylates thus administration of $NaHCO_3$ is recommended in salicylate intoxication. In severe toxicity hemodialysis has to be used as soon as possible to accelerate drug elimination.

Alkali therapy is generally recommended at pH under 7,1-7,0. In acute cases $NaHCO_3$ is given intravenously in 8.4% (1 M) or 4.2% (0.5 M) solution. Normalization of the pH or HCO_3^- should be avoided. Sodium load and a consequential fluid overload should be taken into account. Administration of $NaHCO_3$ can lead to hypokalemia.

Metabolic alkalosis.

Metabolic alkalosis is secondary to acid loss from the gastrointestinal tract or in the urine, or alkali load.

Under normal conditions the kidneys rapidly excrete the HCO^- excess. Thus, for persisting metabolic alkalosis, there must be present some additional ("sustaining") factors, that prevents excretion of the excess bicarbonate in the urine (e.g. decrease the filtration, or increase the reabsorption or the generation of HCO_3^-.). These factors are usually as follows: hypovolemia, hypokalemia, chloride depletion, hyperaldosteronismus (primary or secondary) and reduced GFR.

The most common causes of metabolic alkalosis are shown in Table.

Table: Causes of metabolic alkalosis

<table>
<tr><td>
1) Metabolic alkalosis due to H-ion loss.

   a) Gastrointestinal loss
          1. Vomiting
          2. Nasogastric suction
   b) Excessive use of loop or thiazid diuretics
   c) Primary tubular defects
          1. Bartter's-syndrome
          2. Gitelman's-syndrome
   d) Mineralocorticoid excess

2) Metabolic alkalosis due to alkali load
   a) Excessive alkali ingestion and decrease GFR
          1. Excessive $NaHCO_3$ ingestion
          2. Use of other alkali sources or precursors (citrate, acetate, lactate)
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Metabolic alkalosis due to H-ion loss.

Gastrointestinal loss of HCl due to vomiting leads to retention of bicarbonate, resulting in increased urinary bicarbonate. Volume contraction activates the RAAS system (secondary hyperaldosteronism), which results in HCO_3^- reabsorption and H^+- and K^+- secretion in the kidneys. Distal tubular H-ion secretion is enhanced by not only the aldosteron but also by the increased distal tubular delivery of HCO_3^-.

Loop and thiazide diuretics induce natriuresis and chloruresis, which result in volume contraction, secondary hyperaldosteronism, hypokalemia, and metabolic alkalosis.

In minralocorticoid excess aldosteron (primery hyperaldosteronism), other minaralocorticoids or conditions that mimic mineralocorticoid excess (syndrome of apparent mineralocorticoid excess) promote K-loss, metabolic alkalosis, and unlike former ones, induce Na –retention.

Metabolic alkalosis due to alkali load

In renal failure the filtration and thus, the excretion of bicarbonate is reduced due to decreased GFR. Excessive administration of sodium-bicarbonate (PO or IV), or citrate loads (transfusions) etc. can lead to metabolic alkalosis in this situation.

Symptoms

Usually symptoms of the underlying etiology or the accompanying hypokalaemia dominate clinical manifestations. Alkalosis alone, especially severe one, may cause mental confusion, arrhythmias and neuromuscular disturbances. Alkalemia decreases ionized calcium leading to tetany.

Diagnosis

Underlying causes of metabolic alkalosis can often be determined by history taking and physical examination. Assessment of extracellular fluid volume and evaluation of blood pressure are elementary diagnostic procedures. Measurement of urine Cl^- may help in differentiating of renal or extrarenal causes of acid loss.

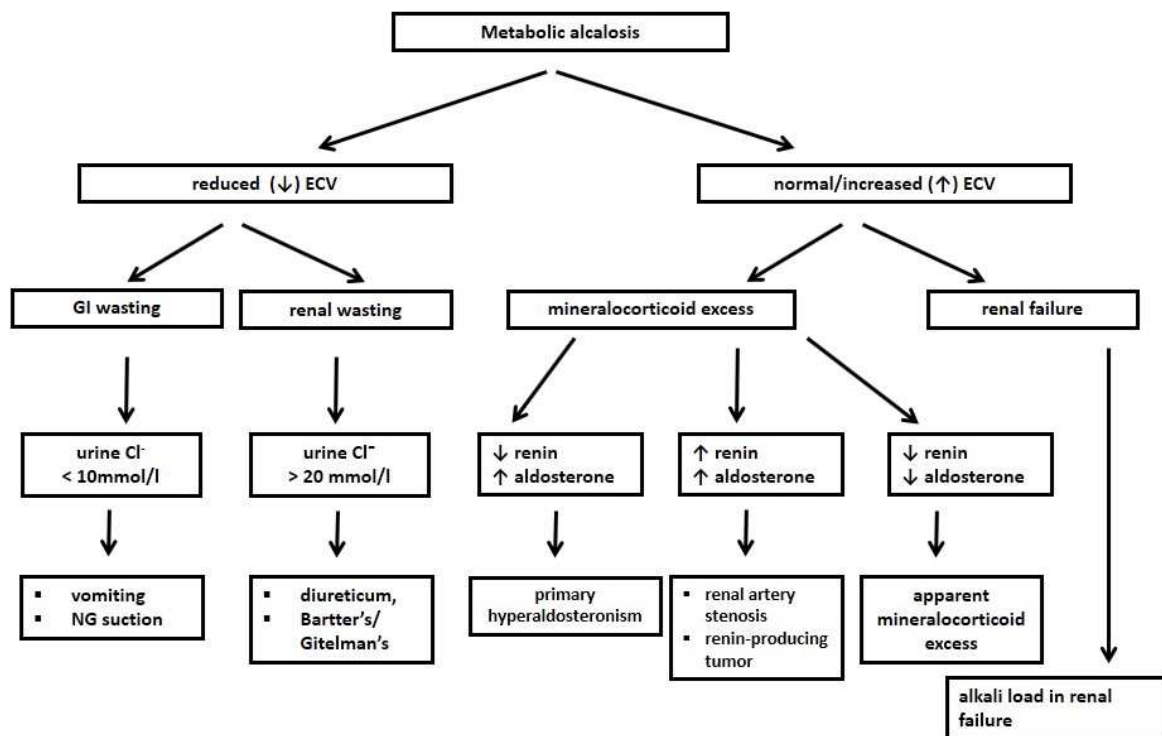Figure shows the approach to the diagnosis of metabolic alkalosis

Figure: Differential diagnosis of metabolic alkalosis.

Treatment

The underlying etiology should be treated primarly. This includes treating the cause of vomiting, administration of antiemetics stopping drugs that induce metabolic alkalosis (e.g.sodium-bicarbonate, sodium- citrate, diuretics, etc.), surgical intervention in adrenal adenoma, or endovascular procedures at renal artery stenosis etc. The second aspect of treatment is focusing on the elimination of the "sustaining" factors such as hypovolemia, hypokalemia etc.