The kidney is the central filter organ of our body. More specifically, it is the small glomeruli that filter those substances from the blood that have to be excreted and thus produce the primary urine. Various factors may cause damages to the glomeruli, resulting in a malfunctioning filtration process. The type of malfunction can vary, and accordingly, so do its clinical manifestations. Differentiating these variable clinical presentations of glomerulonephritis is for many medical students a rather challenging task. The following article will help you to understand the difficult topic of glomerulonephritides.

Introduction

Glomerulonephritis refers to an immune-mediated inflammation of the renal glomeruli. Primary forms can be distinguished from secondary forms; secondary forms occur as part of various systemic diseases. Patients with glomerulonephritis will present with varying symptoms, depending on the pathology.
This article addresses damages to the renal **glomeruli**. In order to gain an understanding of the various possible dysfunctions and their clinical manifestations, we will first take a look at the structure of the glomeruli. The structure of the filtration membrane consists of three layers:

- Fenestrated capillaries
- Glomerular basement membrane
- Visceral layer of the Bowman’s capsule

The endothelium of the capillaries is covered with negatively charged proteoglycans and glycosaminoglycans. The glomerular basement membrane connects the capillaries and the surrounding Bowman’s capsule. It is made up of a dense meshwork that forms a fine mechanical filtration barrier; and like the capillary endothelium, it is covered with proteoglycans and is thus negatively charged. The cells of the visceral layer of the
Bowman’s capsule are called podocytes, whose processes also form a kind of meshwork.

Because of this tight meshwork, large molecules or even cells cannot find a way into the primary urine. In addition, the negative charge prevents the filtration of anions like albumin.

If, however, this filtration barrier is damaged, then these kinds of elements (cells, albumin, macromolecules) can filter into the primary urine and get excreted. With an ongoing decay of the glomeruli, the kidney will lose its ability to produce urine—eventually resulting in renal insufficiency. Glomerular defects can have a variety of causes.

An important distinction is to be made between glomerulonephritis and non-inflammatory glomerular disease. In the present article, the focus is on the description of glomerulonephritis. Further discussions of non-inflammatory causes, such as mechanical (e.g., hypertensive nephropathy), metabolic (e.g., diabetic nephropathy), or vascular (e.g., thrombotic microangiopathy) factors, can be found in their respective articles.

There are various autoimmune causes of glomerulonephritis:

- **IgG antibodies** against the Goodpasture antigen of the basement membrane cause an inflammation reaction that is mediated by antibodies. The Goodpasture antigen is also found in the alveolar basement membrane.
- **Immune complexes** that are formed due to an infection or an autoimmune disease attach to the capillary walls.
- **Anti-neutrophil cytoplasmic antibodies (ANCA)** interact with components of the neutrophil granules and thereby produce glomerular damage.

All immune mechanisms start a pro-inflammatory immune cascade with a subsequent inflammatory reaction. This inflammatory reaction eventually leads to a damage of the glomerular capillary wall. This causes bleeding into the Bowman’s capsule and thus into the primary urine. The renal corpuscle then becomes necrotic and loses functionality. The more glomeruli are affected the more overall kidney function is lost with a decreasing glomerular filtration rate.

Note: The urinary sediment is typically notable for a mild, unselective proteinuria, a microhematuria with dysmorphic RBCs (acanthocytes), and red blood cell casts. This constellation is referred to as nephritic sediment!

**Diagnostic Tests of Glomerulonephritis**

Include urinalysis and kidney biopsy:

**Hematuria:** In a urinalysis, the urinary sediment is examined, and a distinction is made between hematuria, hemoglobinuria, and myoglobinuria. A count of >5 red blood cells/μl of urine, without any red coloring of the urine, is considered a microhematuria. When there is any red color in the urine, it is considered a macrohematuria. Red blood cells may look dysmorphic in the sediment. The abnormal shaping is formed when the cells travel through the tubule system and are exposed to osmotic pressures. An example is
Acanthocytes—RBCs that resemble a Mickey Mouse face.

**Proteinuria:** Typically, there are only small amounts of proteins in the excreted urine. A protein excretion of >150 mg/d is considered proteinuria. The amount of pathological protein excretion can be an indicator of what is causing the disease.

<table>
<thead>
<tr>
<th>Amount of Protein</th>
<th>Type of Protein</th>
<th>Possible Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 200 mg/l</td>
<td>Albumin</td>
<td>Microalbuminuria as a sign of an early nephropathy; e.g., as part of a hypertensive or diabetic disease.</td>
</tr>
<tr>
<td>≤ 1.5 g/d</td>
<td>Small-molecule proteins:</td>
<td>Tubulopathy</td>
</tr>
<tr>
<td></td>
<td>Large-molecule proteins:</td>
<td>Glomerulopathy</td>
</tr>
<tr>
<td>1.5 g/d - 3.0 g/d</td>
<td>Small- and large-molecule proteins</td>
<td>Chronic glomerulonephritis, transplanted kidney</td>
</tr>
<tr>
<td>&gt; 3.0 g/d</td>
<td>Large-molecule proteins</td>
<td>Nephrotic syndrome</td>
</tr>
</tbody>
</table>

Based on: Herold, G und Mitarbeiter, Innere Medizin, 2014

**Important note for clinical practice:** The dipstick only detects a macroalbuminuria of >200 mg/l. For more specific issues (e.g., when suspecting Bence-Jones proteins or a microalbuminuria), more specific quick tests or electrophoretic analyses are required.

**Glucosuria:** An adult person excretes not more than 60 mg of glucose per day. A pathological increased glucose content in the urine occurs when the glucose threshold (about 160 - 180 mg/dl) is exceeded. This might happen due to a diabetes mellitus disease. Glucosuria with normal blood glucose can occur during a pregnancy or in case of a tubular kidney disease.

**Casts:** Casts are cylindrical structures that are formed in the tubules and thus point to their renal origin. The most common hyaline casts can be seen in healthy individuals as well as in individuals with a glomerular disease, which makes them a rather unspecific indicator. The presence of red blood cell casts is strongly indicative of a glomerulonephritis; white blood cell casts are indicative of (chronic) pyelonephritis.

**Immunology:** Testing for various antibodies is helpful for the etiological classification of, e.g., a glomerulonephritis. The specific antibodies will be mentioned below for each type of glomerulonephritis. For the sake of economic practice, not all of the antibodies should be determined right away when a glomerulonephritis is suspected.

**Imaging:** Color duplex sonography is a non-invasive technique and provides many insights for renal assessment. Further structural information can be gathered from CT scans and MRIs. Often, these procedures are combined with angiographic methods.

**Histology:** The definitive confirmation of diagnosis for typing of the glomerulonephritis can only be achieved with a kidney biopsy! Especially when there is the need for immediately finding the correct treatment approach due to a rapid and dramatic progression of the disease, a kidney biopsy will often be a life-saving method.

**Types of Glomerulonephritis**

Based on common clinical manifestations:

- Local glomerulonephritis
- Rapidly progressive glomerulonephritis
- Glomerulonephritis (and other diseases) that lead to the nephrotic syndrome
Local Glomerulonephritis

This group includes Berger disease (immunoglobulin A nephropathy), hereditary glomerulonephritides, and acute, post-infectious glomerulonephritis. There is also minimal change disease, the membranous glomerulonephritis, the membranoproliferative glomerulonephritis, and the focal segmental glomerulonephritis; however, they often develop as part of a systemic disease. Typically, these 4 diseases lead to the nephrotic syndrome and are discussed more in the corresponding section below.

Immunoglobulin A Nephropathy (Berger Disease)

IgA nephropathy is the most common primary glomerulonephritis worldwide. Its etiology is usually idiopathic; but, it is also associated with other diseases such as celiac disease, Crohn’s disease, Henoch-Schönlein purpura, rheumatoid arthritis, systemic lupus erythematoses, or IgA gammopathies. IgA nephropathy can also be preceded by an non-specific infection.

Pathophysiology and Clinical Manifestation of IgA Nephropathy

The IgA immune complexes accumulate in the mesangium of the glomeruli and provoke an inflammatory response. Other accumulation patterns may also develop which can result in a rapidly progressive glomerulonephritis (subendothelial deposits) or a nephrotic syndrome (subepithelial deposits). Typically, the affected patients have micro- (or macro-) hematuria. Sometimes, they present with hypertension, and, in rare cases, with side pain. Rapidly progressive glomerulonephritis or nephrotic syndrome exhibit different clinical manifestations (see below).

Diagnosis is done with kidney biopsy to identify IgA complexes.

Treatment and Prognosis of IgA Nephropathy

Generally, IgA nephropathy has a good prognosis with regular spontaneous remissions. Nevertheless, the risk of a progressive loss of kidney function with imminent end-stage renal failure increases with the extent of the glomerular damage. Treatment approaches are based on symptom manifestation and proteinuria:

- **Proteinuria < 1g/d and normal creatinine**: No treatment necessary. Possible hypertension should be treated with ACE inhibitors.
- **Proteinuria > 1g/d**: Here, treatment with ACE inhibitors is imperative.
- **Proteinuria > 1g/d and increasing renal insufficiency**: Stopping the immunological processes is attempted by administering glucocorticoids or possibly azathioprine/cyclophosphamide in order to prevent irreversible damages.

Hereditary Glomerulonephritis

There are various glomerulonephritis conditions with familial predisposition that are notable for microhematuria. With ongoing persistence, proteinuria develops and eventually an increasing renal insufficiency.
Benign hematuria: Thin basement membrane disease
- Alport syndrome: Hereditary nephritis

Acute Post-Infectious Glomerulonephritis

Especially children in countries with poorly equipped health systems are affected by acute post-infectious glomerulonephritis. In developed countries, this disease has become rare.

Etiology and Pathophysiology of Acute Post-Infectious Glomerulonephritis

This disease is an (immune complex) nephritis that occurs after an infection (usually group B beta-hemolytic streptococci). An endocapillary, proliferative glomerulonephritis develops due to the production of antibodies against the glomerular structures.

Clinical Manifestation and Diagnosis of Acute Post-Infectious Glomerulonephritis

Presence of a possible streptococcus infection has to be determined (pharyngitis, erysipelas, tonsillitis, impetigo, etc.). After these symptoms have subsided, 50% of patients again report feeling sick. This might be non-specific (“the flu”) or characterized by hematuria, hypertension, and edema.

The urinary sediment has to be examined. ASO titer and anti-DNAse-B titer indicate a previous streptococcal infection. The complement consumption of the immune complexes leads to a reduction of C3 complement. For the assessment of renal function, urea and creatinine should be checked regularly during the course of the disease.

Treatment and Prognosis of Acute Post-Infectious Glomerulonephritis

Besides physical rest and a low-salt and low-protein diet, antibiotic aftercare of the infection with 10 days of penicillin is necessary. Hypertension or edema should be treated symptomatically.

Children usually make a complete recovery. Adults frequently experience a persisting impairment of kidney function. Often, some urine anomalies such as proteinuria or hematuria persist. Long-term follow-up should be done in order not to miss any possible late renal damages.

Rapidly Progressive Glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN) is rare. It causes a dramatic decrease in renal function with imminent renal failure and is highly lethal.

Etiologic Types of RPGN

With about 10% of cases, type 1 is the rarest variant: Here, antibodies against the Goodpasture antigen of the basement membrane are formed. Since this antigen is also a
part of the alveolar basement membrane, severe damage to the kidney and lungs with hemoptysis is the consequence. This disease frequently affects young males.

**Type 2** makes up about 40% of cases: Here, immune complexes accumulate on the basement membrane. These immune complexes may be post-infectious or caused by an antibody-producing underlying disease (e.g., SLE, Henoch-Schönlein purpura).

With about 50% of cases, **type 3** is the most common type: Here, ANCA-associated vasculitides are the cause. Histologically, there are no accumulations. The antibodies are directed against enzymes (e.g., myeloperoxidase for pANCA or antiprotease 3 for cANCA). This antibody production is precipitated, for instance, by a granulomatosis with polyangiitis (Wegener’s disease) or by a microscopic polyangiitis. Another possible cause is Churg-Strauss disease.

**Clinical Manifestation and Diagnosis of RPGN**

The diseased individuals are exhausted and pale. Often, hypertension can be noticed. A strong proteinuria with the corresponding symptoms (see below) can develop; in most cases, however, nephritic sediment can be found. Pulmonary symptoms have to be taken into account. Kidney biopsy should be done if this disease is suspected. Histologically, there is an extracapillary, proliferative inflammatory reaction with Demilune formation of the glomeruli.

**Image**: “Fine tissue slice of a RPGN” by KGH. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0)

**Treatment of RPGN**

Treatment is based on the underlying cause and the severity of the disease. Standard treatments include glucocorticoids in high dosages (1g/day i.v.) and cyclophosphamide.
For treating Goodpasture syndrome, plasmapheresis can additionally be used over the course of 2 – 3 weeks in order to eliminate the antibodies. After the treatment with glucocorticoids and cyclophosphamide has been tapered off, aftercare consists in the administration of azathioprine for 6 – 12 months. Type 2 and type 3 RPGN have to be treated longer and with more regularity because they tend to recur.

If treatment is provided early and correctly, renal function can be improved and recovered.

Nephrotic Syndrome

The nephrotic syndrome is defined by:

- severe proteinuria of more than 3g/day
- hypoproteinemia
- hypoalbuminemia-related edema
- hyperlipoproteinemia (especially cholesterol and triglycerides)

Pathophysiology of Nephrotic Syndrome

The nephrotic syndrome develops out of a disturbed glomerular filtration barrier which makes the glomerulus abnormally permeable. The filter acts no longer selectively, yet the glomerular perfusion in itself remains functional. This produces a large amount of large-molecule proteins in urine.

**Note:** A severe proteinuria develops with initially normal GFR and creatinine parameters and **without** hematuria. These urinary findings are describes as **nephrotic sediment**.

Etiology

These forms are the most common:

**Minimal Change Disease:** Minimal lesions of the glomerulus, that can only be made visible under the electron microscope, are the most common cause of nephrotic syndrome in children (>90% of cases). This disease is idiopathic. It causes diffuse damage to the podocytes.

**Membranous glomerulonephritis:** most common cause in adults and caused by formation of immune and complement complexes. These complexes either have an idiopathic origin or develop in relation to infections (hepatitis B, HIV, syphilis, malaria), autoimmune diseases, or pharmaceuticals. Histology shows deposits of complexes on the glomerular basement membrane.

Membranoproliferative glomerulonephritis or the focal segmental glomerulonephritis can also cause nephrotic syndrome.

**Note:** Other systemic (non-infectious) diseases can also cause nephrotic syndrome. One very frequent disease that should be kept in mind is diabetes mellitus. Other diseases include amyloidosis or a plasmocytoma.

Clinical Manifestations of Nephrotic Syndrome
In cases of a mild dysfunction, the liver can usually compensate for any protein losses. If the filtration dysfunction becomes too severe, certain protein losses will become noticeable, which directly relate to clinical symptoms and are therefore easy to remember:

- **Immunoglobulin loss** leads to an increased susceptibility to infections.
- **Antithrombin-III loss** results in an increased susceptibility to thrombosis with, e.g., pulmonary embolism, renal vein thrombosis, or cerebral vein thrombosis.
- **Albumin loss (+IgG and ATIII loss)** causes the colloid osmotic pressure to decrease, and edema develops. For differential diagnosis, it is helpful to remember that this edema is caused by a protein deficiency, not gravity (cardiogenic edema), so it can be found anywhere on the body (= anasarca).
- In an advanced stage, **renal insufficiency** can occur.

### Diagnosis of Nephrotic Syndrome

Serum electrophoresis reveals a characteristic loss of albumin and gamma fraction with a relative increase of the alpha-2 and beta fraction. The gold standard for diagnosis is the kidney biopsy.

### Treatment of Nephrotic Syndrome

Include glucocorticoids and immunosuppressives (cyclosporine, cyclophosphamide). Physical rest and a low-protein and low-salt diet is recommended. Increased risk for thrombophilia has to be taken into account and be counteracted with thrombosis prophylaxis. Thromboembolic complications must be met with effective anticoagulation (antithrombin-III deficiency does not respond to heparin).

### Review Questions

Solutions can be found below the references.

1. A 50-year-old amateur biker had an accident 3 years ago which resulted in a
chronic osteomyelitis of the femur. Due to the relieving posture he adopted, he suffers under frequent lower back pain for which he has been taking indometacin repeatedly in the last week. The pain is persistent which is why he now has come to the emergency department. You notice a serum creatinine concentration of 2.0 mg/dL, and in the urinary sediment, you observe red blood cell casts.

What has most likely caused his renal failure?

A. Amyloidosis
B. Peri (post)-infectious glomerulonephritis
C. Analgesics nephropathy
D. Acute NSAID-induced prerenal renal failure
E. Acute NSAID-induced intrarenal renal failure

2. The rapidly progressive glomerulonephritis...

A. ...is the most common renal disease in young females.
B. ...leads within a few weeks or months to end-stage renal failure if left untreated.
C. ...is treated with 3rd generation cephalosporins.
D. ...can be safely diagnosed using native ultrasound.
E. ...can be healed in most cases through treatment with methotrexate.

Matthew P. presents with microhematuria. Which of the following would most likely indicate that the cause of this patient's microhematuria is of glomerular nature?

A. Occurrence of microhematuria in midstream urine
B. The simultaneous occurrence of hyaline casts
C. The simultaneous occurrence of acanthocytes
D. The simultaneous occurrence of leucocyturia
E. The simultaneous occurrence of glucosuria

References


Correct Answers: 1B, 2B, 3C

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