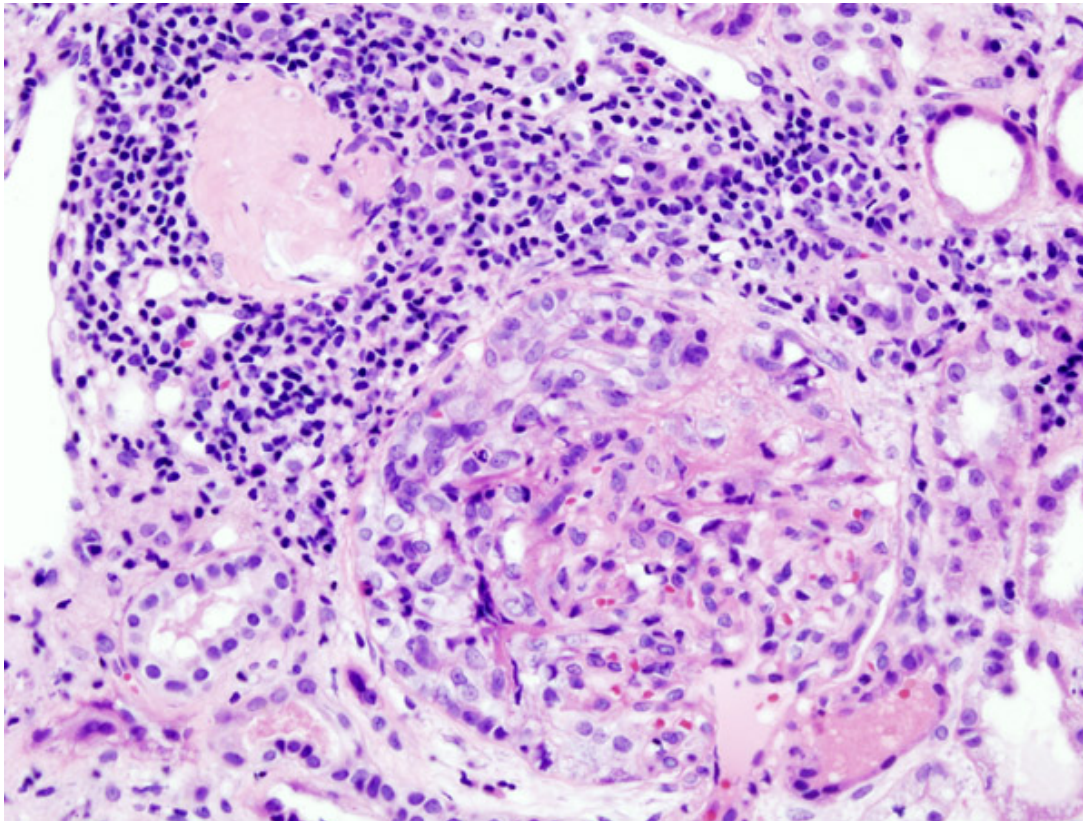


Glomerulonephritis — Symptoms and Treatment

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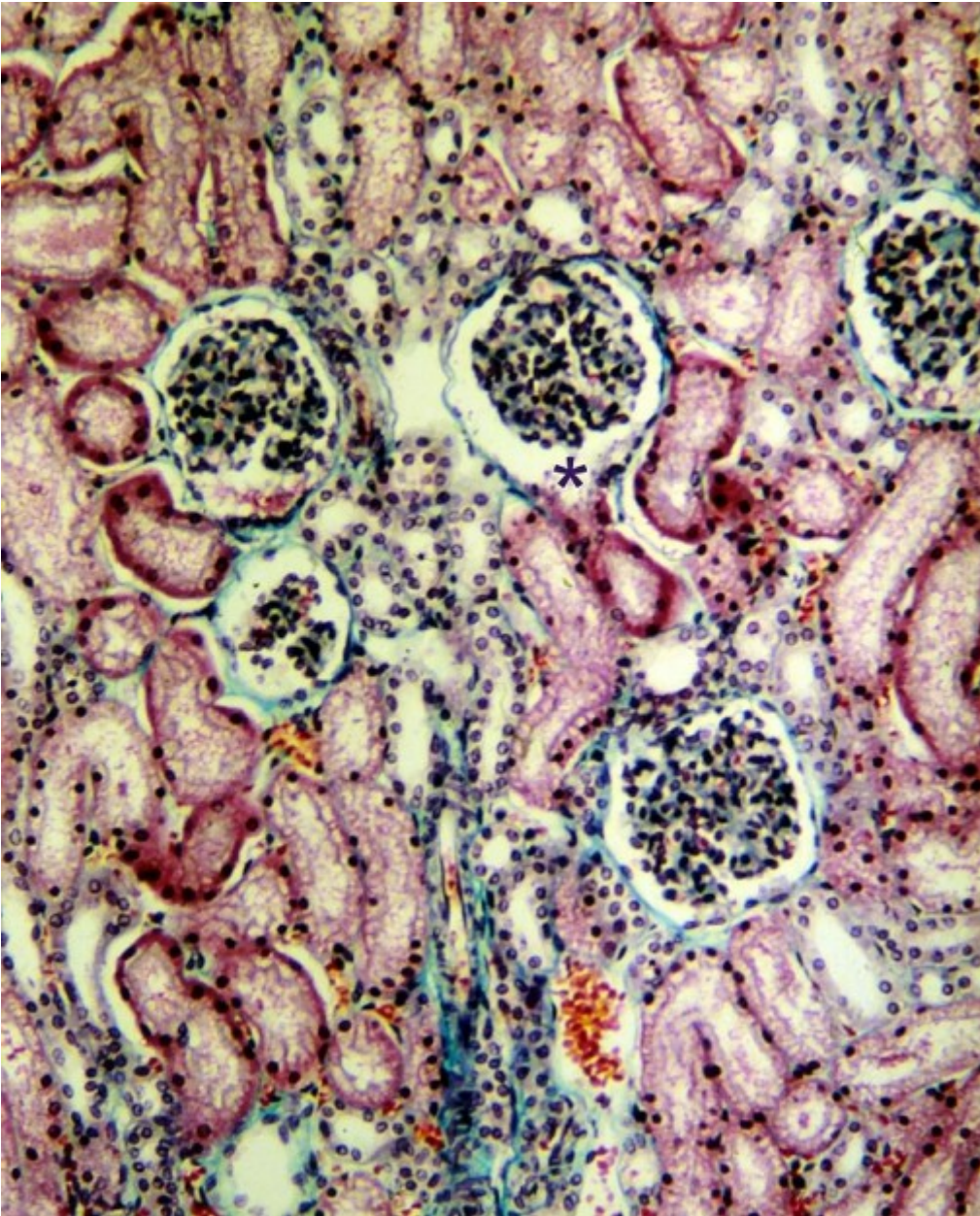
The kidney is the central filter organ of our body. More specifically, small glomeruli filter out substances from the blood that need to be excreted and thus produce the primary urine. Various factors may cause damages to the glomeruli, resulting in a malfunctioning filtration process. The type of malfunction 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 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.

Pathophysiology



[Image](#): Light microscopic sectional image of the renal cortex. By Rollrobooter, License: [CC BY-SA 3.0](#)

Damage to the renal **glomeruli** is contributory to renal dysfunction. In order to understand 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 3 layers:

- Fenestrated capillaries
- Glomerular basement membrane
- Visceral layer of 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 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.



Image: Diagram of renal corpuscle structure: A – Renal corpuscle B – Proximal tubule C – Distal convoluted tubule D – Juxtaglomerular apparatus 1. Basement membrane (Basal lamina) 2. Bowman's capsule – parietal layer 3. Bowman's capsule – visceral layer 3a. Pedicels (Foot processes from podocytes) 3b. Podocyte 4. Bowman's space (urinary space) 5a. Mesangium – Intraglomerular cell 5b. Mesangium – Extraglomerular cell 6. Granular cells (Juxtaglomerular cells) 7. Macula densa 8. Myocytes (smooth muscle) 9. Afferent arteriole 10. Glomerulus Capillaries 11. Efferent arteriole. By M.Komorniczak, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

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 ongoing damage to 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** 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 produce glomerular damage.

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

Note: Urinary sediment is typically notable for mild, unselective proteinuria, microhematuria with dysmorphic RBCs (acanthocytes), and RBC casts. This constellation is referred to as nephritic sediment!

Diagnostic Tests

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 RBCs/ μ L of urine without any red coloration of the urine is considered microhematuria. When there is any red color in the urine, it is considered macrohematuria. RBCs may look dysmorphic in the

sediment. 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, only small amounts of protein are in 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.

Amount of Protein	Type of Protein	Possible Cause
20-200 mg/L	Albumin	Microalbuminuria as a sign of early nephropathy; e.g., as part of hypertensive or diabetic disease
≤ 1.5 g/day	Small-molecule proteins: Large-molecule proteins:	Tubulopathy Glomerulopathy
1.5 g/d-3.0 g/day	Small- and large-molecule proteins	Chronic glomerulonephritis, a transplanted kidney
> 3.0 g/day	Large-molecule proteins	Nephrotic syndrome

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

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

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

Casts: Casts are cylindrical structures that are formed in the tubules and thus point to their renal origin. Hyaline casts are the most common type of casts and can be seen in healthy individuals as well as in individuals with glomerular disease. This makes them a rather nonspecific indicator. The presence of RBC casts is strongly indicative of glomerulonephritis. WBC casts are indicative of (chronic) pyelonephritis.

Immunology: Testing for various antibodies is helpful for the etiological classification of glomerulonephritis. The specific antibodies will be mentioned below for each type of glomerulonephritis. For economic reasons, not all of the antibodies should be determined right away when 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 typing of glomerulonephritis can only be achieved with a kidney biopsy, especially when immediate findings are needed to administer correct treatment due to the rapid progression of the disease. Here, a kidney biopsy will often be a life-saving method.

Types of Glomerulonephritis

The various types of glomerulonephritis can usually be divided into proliferative or non-proliferative types. The proliferative types of glomerular disease lead to a nephritic syndrome, while the non-proliferative types of glomerular disease lead to a nephrotic

syndrome:

- **Proliferative:** acute, post-infectious glomerulonephritis, IgA nephropathy or Berger's disease, granulomatosis with polyangiitis or Wegener's disease, microscopic polyangiitis, Churg-Strauss syndrome, Goodpasture syndrome or anti-GBM disease, Alport syndrome, thin basement membrane disease, rapidly progressive glomerulonephritis (RPGN), and lupus nephritis.
- **Non-proliferative:** Minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis (can present with both nephrotic and nephritic syndromes), diabetic nephropathy, AL amyloidosis, light-chain deposition disease, and lupus nephritis.

The most important types of glomerulonephritis are explained below.

Immunoglobulin A Nephropathy (Berger's Disease)

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

Pathophysiology and Clinical Manifestation

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 rapidly progressive glomerulonephritis (RPGN)(sub**endo**thelial deposits) or nephrotic syndrome (sub**epi**thelial deposits). Typically, the affected patients have micro- (or macro-) hematuria. Sometimes, they present with hypertension, and, in rare cases, with side pain. RPGN and nephrotic syndrome exhibit different clinical manifestations (see below).

Diagnosis is made with a kidney biopsy to identify IgA complexes.

Treatment and Prognosis

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 glomerular damage. Treatment approaches are based on symptom manifestation and proteinuria:

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

Hereditary Glomerulonephritis

There are various glomerulonephritic conditions with a familial predisposition, which are notable for microhematuria. With ongoing persistence, proteinuria develops and

eventually presents with increasing renal insufficiency.

- **Benign hematuria: Thin basement membrane disease**
- **Alport syndrome: Hereditary nephritis**

Acute Post-Infectious Glomerulonephritis

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

Etiology and Pathophysiology

This disease is immune complex-mediated nephritis that occurs after infection (usually group A beta-hemolytic streptococci). Endocapillary proliferative glomerulonephritis develops due to the production of antibodies against the glomerular structures.

Clinical Manifestation and Diagnosis

The presence of a possible streptococcus infection has to be determined (pharyngitis, erysipelas, tonsillitis, impetigo, etc.). After these symptoms have subsided, 50% of patients report ill health again. This might be non-specific (flu-like symptoms) 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

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 conducted in order to identify any possible late renal damages.

Rapidly Progressive Glomerulonephritis

RPGN is rare. It causes a marked decrease in renal function with imminent renal failure and is highly lethal.

Etiologic Types

Presenting in 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 occurs. 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, and 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 granulomatosis with polyangiitis (Wegener's disease) or by microscopic polyangiitis. Another possible cause is Churg-Strauss disease.

Clinical Manifestation and Diagnosis

Diseased individuals are exhausted and pale. Often, hypertension can occur. Strong proteinuria with corresponding symptoms (see below) can develop. In most cases, however, nephritic sediment can be found. Pulmonary symptoms have to be taken into account. A kidney biopsy should be performed if this disease is suspected. Histologically, there is an extracapillary, proliferative inflammatory reaction with Demilune formation of the glomeruli.

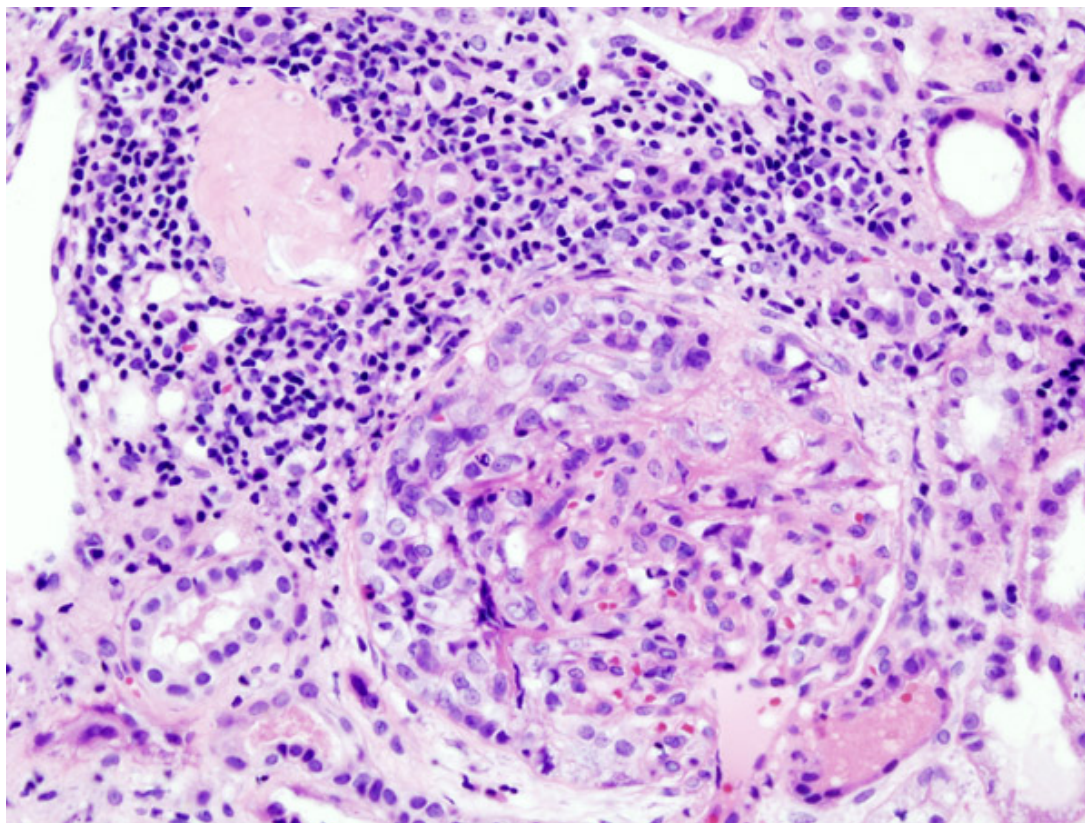


Image: Fine tissue slice of RPGN. By KGH, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Treatment

Treatment is based on the underlying cause and severity of the disease. Standard treatments include glucocorticoids in high dosages (1 g/day IV) and cyclophosphamide. For 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 of 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

Nephrotic syndrome is defined by:

- Severe proteinuria of > 3 g/day
- Hypoproteinemia
- Hypoalbuminemia-related edema
- Hyperlipoproteinemia (especially cholesterol and triglycerides)

Pathophysiology

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

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

Etiology

These forms are the most common:

Minimal change disease: Minimal lesions of the glomerulus, which can only be made visible under an 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: This is the most common cause of nephrotic syndrome in adults and is due to the formation of immune and complement complexes. These complexes either have an idiopathic origin or develop in relation to infections (hepatitis B virus, HIV, syphilis, malaria), autoimmune diseases, or pharmaceuticals. Histology shows deposits of complexes on the glomerular basement membrane.

Note: Membranoproliferative glomerulonephritis or focal segmental glomerulonephritis can also cause nephrotic syndrome. Other non-infectious, systemic 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 plasmacytoma.

Clinical Manifestations



Image: Plasmodium falciparum nephrosis edema.
By Patho, License: Public Domain

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

- **Immunoglobulin loss** leads to increased susceptibility to infections.
- **Antithrombin-III loss** results in increased susceptibility to thrombosis (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 (e.g., cardiogenic edema), so it can be found anywhere on the body (anasarca).
- In an advanced stage, **renal insufficiency** can occur.

Diagnosis

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 a kidney biopsy.

Treatment

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

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