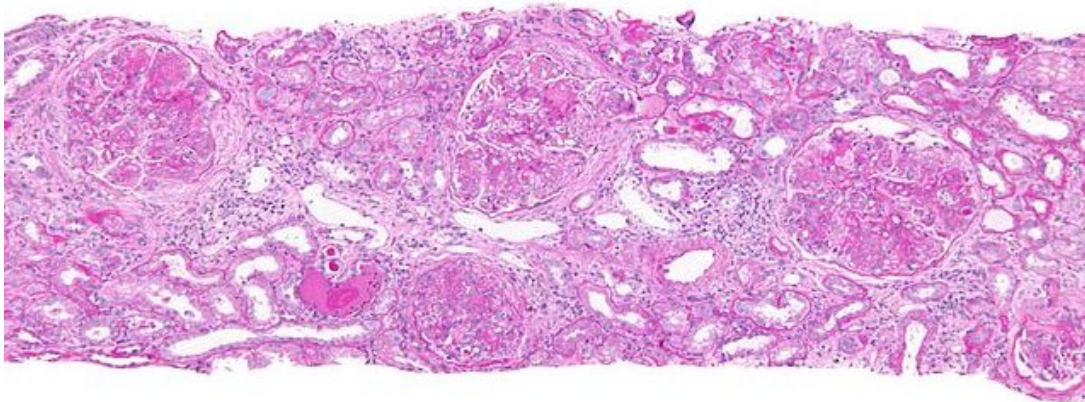


# Membranoproliferative Glomerulonephritis (MPGN) — Prognosis and Treatment

[See online here](#)

**Membranoproliferative glomerulonephritis (MPGN) is a type of immune-mediated glomerular disease. The name is an indication of its pathology, with thickening of the basement membrane and proliferative changes. MPGN is categorized into three types: type I, type II (also called dense deposit disease) and type III. Students should be familiar with an overview of this condition, including the pathological features that set it apart from other glomerular disorders, as well as the diagnostic approach and management of MPGN.**



## Definition

Membranoproliferative glomerulonephritis (MPGN) is a **pattern of glomerular injury** that is caused by an **immune-mediated reaction**. The disease process involves **thickening of the glomerular basement membranes** and **proliferative changes**, including **hypercellularity of the glomerulus** and **increased mesangial matrix**.

Other names for MPGN include mesangiocapillary glomerulonephritis and lobar glomerulonephritis.

## Epidemiology of Membranoproliferative Glomerulonephritis (MPGN)

MPGN is a **rare glomerular disease** and seems to be **decreasing in prevalence**. Most patients who present with primary MPGN are adolescents or young adults – over 75% of cases are diagnosed in patients aged 8 to 16. Also, 10 % of cases of nephrotic syndrome that occur in children and young adults are caused by MPGN. The secondary membranoproliferative disease is more common than an idiopathic disease.

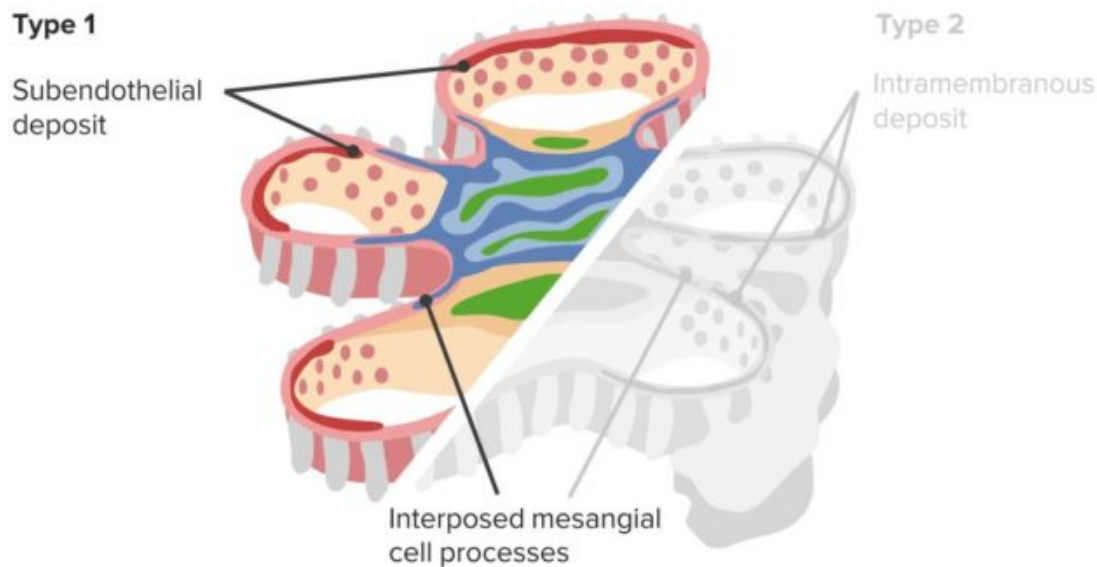
# Classification of Membranoproliferative Glomerulonephritis (MPGN)

MPGN is broadly classified based on etiology into

1) Primary/ idiopathic disease that is further subdivided into three **groups** of disorders based on their structural appearance:

- a. **Type I MPGN** involves the deposition of immune complexes made up of IgG and complement.
- b. **Type II MPGN** is also called dense deposit disease, and complement activation is a key part of this disorder. Type II MPGN falls under a group of disorders known as C3 glomerulopathies. It is characterized by dense deposits in the glomerular basement membrane.
- c. Little is known about **type III MPGN**, which is relatively rarer, so only types I and II MPGN will be the focus of this article. Subepithelial and subendothelial deposits characterized it.

2) A secondary membranoproliferative disease where the cause of the immune reaction is known.



"Membranoproliferative Glomerulonephritis" Image created by Lecturio

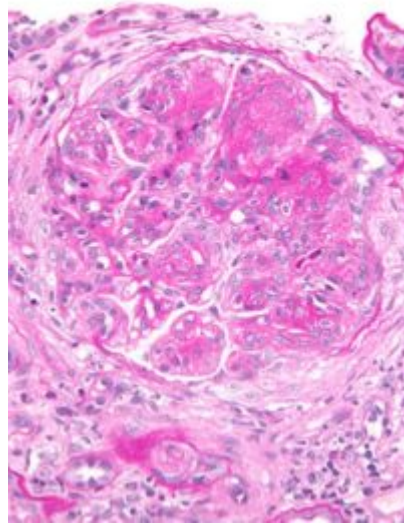
## Etiology of Membranoproliferative Glomerulonephritis

If the etiology of membranoproliferative glomerulonephritis is unknown, then it is called primary or idiopathic MPGN. However, it is thought that **antigens** in primary MPGN originate from **infectious particles**, such as viruses (e.g. hepatitis B and C). These antigens may become lodged within the glomerulus or form immune complexes first and then deposit within the glomerulus.

Cases of secondary MPGN are becoming more common as the cause is being increasingly identified. Disorders associated with secondary MPGN include :

- **Immune complex disorders**, such as [systemic lupus erythematosus](#) and [Henoch-Schönlein Purpura](#),
- **Systemic infections** such as hepatitis B, hepatitis C, endocarditis, chronic abscesses, [Human Immunodeficiency Virus](#) and schistosomiasis.
- **Malignancies** such as chronic lymphocytic [leukemia](#), and  $\alpha$ 1-antitrypsin deficiency.

Cases of type II MPGN are general idiopathic, whereas type 1 MPGN is usually secondary MPGN with an apparent underlying cause of MPGN.



*Image:* "Very high magnification micrograph of membranoproliferative glomerulonephritis. PAS stain. Kidney biopsy." by Nephron - Own work. License: [CC BY-SA 3.0](#)

## Membranoproliferative glomerulonephritis at a cellular level

The name of MPGN offers a clue about its histopathology. Primary features include **thickening of the glomerular basement membrane** ("membrano") and **glomerular cell proliferation or hypercellularity** ("proliferative"). Glomerular cell proliferation includes cells of the **mesangium** and **capillary endothelium**, as well as an **infiltration of leukocytes**, including neutrophils and mononuclear cells.

Deposits are present in the **capillary walls** and **mesangial regions** of the glomerulus. **Crescent cells** may also be present within **Bowman's spaces**. Numerous crescent cells appear when MPGN evolves into rapidly progressive **glomerulonephritis**.

The thickened glomerular capillary basement membrane resembles a **"tram-track" appearance** on light microscopy with certain stains such as the Periodic Acid Schiff stain. There is also a **"splitting"** or duplication of the basement membrane with cellular components present in between the duplicated membrane.

While **type I MPGN** and **type II MPGN** share a **similar morphology**, there is a difference in the composition of these deposits. In type I MPGN, the deposits are composed of **immune complexes**. Immune complexes are formed when there is an

**inappropriate production of antibodies** in response to a nephritogenic antigen. Circulating immune complexes then deposit in the glomerulus, resulting in complement activation and this triggers a **cascade of inflammatory events**. Type 1 MPGN involves activation of classical and alternative complement pathways.

It should be noted that the deposits in type I MPGN are **primarily subendothelial deposits**, but there may be **mesangial** and **subepithelial** deposits too.

In type II MPGN, the deposits are composed of an **unknown material**. In contrast to type I, type II MPGN mostly features **ribbons of dense intramembranous deposits**. In type II MPGN, complement activation also plays a key role, but the complement is present only in the glomerular basement membrane and not in the deposits.

## Symptoms of Membranoproliferative Glomerulonephritis

MPGN can present with features of nephrotic syndrome :



Image: "Nephrotic syndrome causing edema." by CharlesPicavet - Own work. License: Public Domain

- [Proteinuria](#)
- [Hematuria](#)
- [Edema](#)
- [Hypertension](#)

Patients may present with **nephrotic syndrome**, **nephritic syndrome**, or **asymptomatic proteinuria and hematuria**.

Asymptomatic proteinuria and hematuria that is detected on routine urinalysis screening.

Most patients (about 50 %) present with signs and symptoms of **nephrotic syndrome**, which is characterized by **massive proteinuria** (> 3.5 g/24 hours), hypoalbuminemia, **edema**, and [hyperlipidemia](#).

**Asymptomatic proteinuria** (that is not in the nephrotic range) **and hematuria** is the primary presentation in 25 % of cases. In another 25 % of cases, patients present with

an **acute nephritic syndrome with hypertension, proteinuria, hematuria, and periorbital edema**.

The **variability of the clinical presentation of MPGN** mirrors the disease process. During the initial acute injury and proliferative phase, patients may present with a nephritic picture. Later, with disease progression and reparative changes, patients present with nephrotic syndrome. The presentation may also be influenced by the type of MPGN.

Patient state of nephritic/ nephrotic syndrome may worsen to chronic renal failure where some patients present with azotemia.

## Diagnosis of Membranoproliferative Glomerulonephritis (MPGN)

Clinical and laboratory findings are **non-specific** as there is a wide range of causes of the nephrotic or nephritic syndrome. MPGN is confirmed by a **histological diagnosis** using a **renal biopsy specimen**.

### Lab tests

**Urinalysis** reveals proteinuria and hematuria. Urine microscopy will often show dysmorphic red blood cells (acanthocytes), leukocytes and RBC casts, indicative of glomerulonephritis. 24-hour urinary protein can be measured to quantify the proteinuria or a spot urine protein-to-creatinine ratio. Nephrotic range proteinuria (> 3 g/24 h) is present in about 50 % of cases.

**Blood tests** are also helpful. Some patients will have elevated creatinine and blood urea nitrogen (BUN) levels. A degree of azotemia is present in 50 % of cases, but it is the patients presenting with the nephritic syndrome who often have significantly reduced GFR. Complement levels should also be ascertained since hypocomplementemia can occur in all types of MPGN. C3 and C4 levels are both reduced in type I MPGN. In type II MPGN, C3 levels are more reduced than C4, as the alternative complement pathway is preferentially activated.

Lab tests should also be done to look for **possible secondary causes of MPGN**. This includes tests, such as **viral serology for hepatitis B and C**, an **autoimmune screen for rheumatological disorders** such as **SLE**, blood cultures for endocarditis, tests for monoclonal gammopathies, including cryoglobulins.

### Imaging

A **renal ultrasound** is usually done prior to a **biopsy**, looking for evidence of **chronic kidney disease**.

Imaging tests may also be done if a certain secondary cause of MPGN is suspected, such as a **chronic abscess**, in which case **CT imaging** may be useful, or **endocarditis**, using an **echocardiogram** for diagnostic confirmation.

### Renal biopsy

A renal biopsy enables a **definitive diagnosis** of MPGN. **Light microscopy** shows glomerular basement membrane thickening and glomerular hypercellularity.

**Immunofluorescence studies** show diffuse intense granular staining of the mesangium and capillary loops with C3, IgG and IgM.

On **electron microscopy**, subendothelial deposits and mesangial deposits are pathognomonic of MPGN (type I). In type II MPGN, dense intramembranous deposits are pathognomonic of this disease process.

## Differential diagnosis of membranoproliferative glomerulonephritis

There are many different types of glomerular disease, either primary or secondary, that can result in a similar presentation of the nephrotic or nephritic syndrome in patients, including:

- **Acute glomerulonephritis** e.g., post-streptococcal glomerulonephritis (often preceded by a streptococcal throat infection; streptococcal antibody titers are positive).
- **Lupus nephritis** (one of the manifestations of the multisystem immune disorder, lupus (SLE). The patient may have other features, best remembered with the **SOAPBRAINMD** mnemonic: serositis, oral ulcers, arthritis, photosensitivity, blood dyscrasias, renal involvement, ANA positive, immunologic phenomena [anti-dsDNA, antiphospholipid antibodies], malar rash, discoid rash).
- **Minimal change disease** (most common cause of nephrotic syndrome in children; “minimal change” with podocyte effacement seen on electron microscopy of the renal biopsy).
- **Focal segmental glomerulosclerosis** (renal biopsy demonstrates focal and segment sclerosis of the glomeruli).
- **Membranous nephropathy.**
- **Diabetic nephropathy** (patient has a long-standing history of [diabetes](#)).
- **IgA nephropathy** (episodic hematuria accompanied by pharyngitis).
- **Rapidly progressive glomerulonephritis** (numerous crescent cells on renal biopsy).

## Therapy of Membranoproliferative Glomerulonephritis (MPGN)

The treatment of **type 1 MPGN** or cases of **secondary MPGN** is with the treatment of the underlying cause, such as **treatment of associated infection** (e.g., hepatitis C), an **autoimmune disorder** (e.g., SLE) or **neoplasm**.

For **type II MPGN**, however, there is **no established treatment** at present. In some cases, **immunosuppressive therapy with steroids** may be trialed. Other drugs, such as anti-platelets (e.g., aspirin, dipyridamole), [anticoagulants](#) (e.g., warfarin) and cytotoxic agents (e.g., cyclophosphamide), have no demonstrated benefit in MPGN.

## Progression and Prognosis of MPGN

The **rule of thirds** is a useful way to remember the prognosis of MPGN. About one-third of patients undergo **spontaneous remission**. One-third experience **persistent symptoms with a variable course** and one-third experience **progressive decline**



## and develop end-stage kidney disease.

Prognosis of MPGN depends on a patient's presentation and clinical features. Those who present with mild proteinuria and asymptomatic hematuria tend to follow a **relatively benign course**. More severe presentations, with heavier proteinuria, nephrotic syndrome, [hypertension](#), advanced azotemia, nephritic syndrome, or the presence of crescents on renal biopsy, follow a **more rapidly deteriorating course**. This is often referred to as rapidly progressive glomerulonephritis.

In 35—60 % of patients, [chronic renal failure](#) occurs after 10 years following diagnosis. However, after 20 years, about 90% of patients develop renal failure.

The prognosis for type II MPGN is poorer than that of type I MPGN. An important contributing factor is the lack of established treatment for type II MPGN (generally primary or idiopathic MPGN).

## Complications of MPGN

1. In 35—60 % of patients, [chronic renal failure](#) occurs after 10 years following diagnosis
2. However, after 20 years, about 90 % of patients develop renal failure
3. Secondary hypertension after the disease is cured
4. Infections especially during immunosuppressive therapy
5. Thromboembolic tendencies are more common
6. Hyperlipidemia
7. Other major complications

## Diabetic Glomerulosclerosis

Increase in proteinaceous material in the wall of the vessels

## Renal Amyloidosis

Congo red-stained section of glomerulus and tubules reveals apple-green birefringence under polarized light in areas with amyloid deposition.

Hematoxylin and eosin-stained slide of a glomerulus show eosinophilic acellular amyloid material in the glomerular tuft and capillary walls.

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