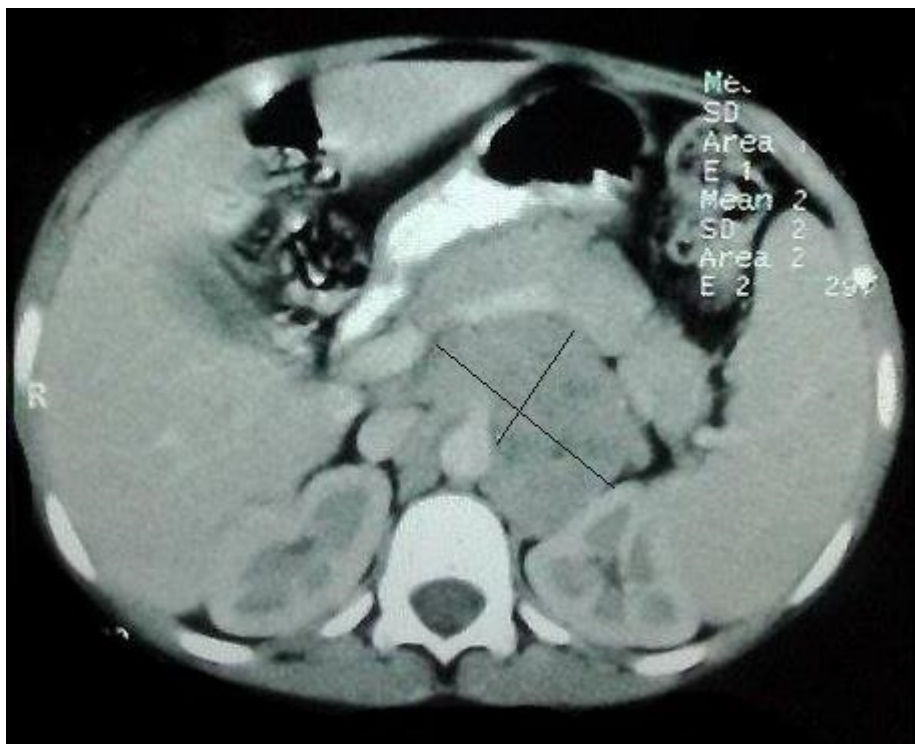


# Pediatric Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Goodpasture Syndrome (GPS)

[See online here](#)

**Granulomatosis with Polyangiitis (GPA) and Goodpasture's syndrome are two similar conditions that are characterized by small vessel disease and are considered autoimmune conditions. Goodpasture's disease, on the other hand, is a different condition from GPA and is characterized by glomerulonephritis with anti-glomerular basement membrane antibodies. Both conditions are rare in children. The prognosis of GPA and Goodpasture's disease has improved dramatically in the last few decades; however, mortality remains high. GPA and Goodpasture's disease present with fever, hemoptysis, shortness of breath, and symptoms and signs is suggestive of kidney disease.**



## Overview

Granulomatosis with polyangiitis (GPA) is a **rare autoimmune disease of unknown etiology** that affects multiple organ systems. The main characteristic of GPA is necrotizing granulomatous inflammation and pauci-immune vasculitis of the small and medium-sized blood vessels.

The condition was previously known as Wegener Granulomatosis; however, the name was

changed because of two main reasons:

**Wegener was a Nazi physician;** therefore, the American College of Rheumatology and the American Society of Nephrology preferred to abandon his name from the terminology.

The American College of Rheumatology is now naming rheumatologic and autoimmune conditions based on the etiology and pathophysiology of the condition, which is believed to result in an **easier to comprehend and remember** nomenclature.

Goodpasture's syndrome is a clinical diagnosis that is **characterized by acute glomerulonephritis and pulmonary alveolar hemorrhage**. The condition is very rare in children and is commonly associated with small vessel disease that is mediated by antineutrophil cytoplasmic autoantibodies (ANCA). Goodpasture's syndrome can be a clinical manifestation of several medical conditions including GPA.

Goodpasture's disease is a specific medical condition that is different from GPA. Goodpasture's disease is **characterized by the presence of anti-glomerular basement membrane (anti-GBM) antibodies**. Anti-GBM antibodies usually show linear deposition on immunohistochemical studies of renal biopsies. This feature is not seen in GPA and can be used to differentiate between the two conditions.

## Epidemiology of Granulomatosis with Polyangiitis and Goodpasture's Syndrome

GPA onset is rarely seen in children. Typically, childhood-onset GPA is **diagnosed in children aged between 4 and 18 years of age**. Most cases of childhood-onset GPA are seen in adolescent girls. On the other hand, adult-onset GPA is more commonly seen in men with a male-to-female ratio of 1.5:1.

**Information about the incidence and prevalence of GPA in children is scarce.**

The estimated incidence of GPA in the general population is 3 cases per 100,000 per year. GPA appears to be more common in people from European descent. GPA is rarely seen in African Americans.

The prognosis of GPA is dependent on the physician's definition of remission and the type of remission induction therapy used. Generally, **one third up to 90% of GPA patients go into remission**.

**Relapse in GPA is quite common** and half of the patients experience a relapse in 5 years post-remission. Older patients, target organ damage, and renal involvement have a direct effect on the survival rate of the patient. Children without renal involvement have a 100% 5-year survival rate. Cardiovascular disease is also more common in patients with GPA.

**The main complications of GPA are:**

- End-stage renal disease
- Pulmonary dysfunction
- Destructive sinus disease
- Perforation of the nasal septum
- Death

**The main causes of death in GPA include:**

- Infection

- Renal failure
- Cardiovascular events
- Respiratory failure

The use of immunosuppressive therapy also puts the patient at an increased risk of developing malignancies.

Goodpasture's disease, also **known as anti-GBM disease, is also rare in children**. Severe Goodpasture's disease appears to be more common in white children. The annual incidence of pediatric Goodpasture's disease is around 1 in one million. Goodpasture's disease is responsible for 1% of end-stage renal disease in children.

Goodpasture's disease has a similar frequency in males and females in children. The **condition is more common in adult males compared to females**, the estimated ratio of 9:1. The median age at the time of diagnosis of childhood-onset Goodpasture's disease is 17 years.

The mortality rate of Goodpasture's disease has **dropped from 96% in the 1960s to 41% in the current era of plasma exchange**. While Goodpasture's disease is characterized by pulmonary alveolar hemorrhage, most patients have a complete recovery from this event. End-stage renal disease is quite common in Goodpasture's disease. Up to 90% of Goodpasture's disease patients are expected to develop an end-stage renal disease.

## Pathology of Granulomatosis with Polyangiitis and Goodpasture's Syndrome

The main pathology seen in GPA is geographic necrosis and granulomatous inflammation of the small and medium-sized blood vessels. **Blood vessels within the airways and the kidneys are the main ones to be affected** which explains why GPA can cause Goodpasture's syndrome.

ANCAs have been implicated in the pathology of GPA. Because of the implication of ANCAs, the condition is believed to be caused by an impaired humoral autoimmune response to an unknown antigen. Cytoplasmic diffuse ANCA known as **C-ANCA is the main abnormality found in immunohistochemical studies of biopsies taken from affected tissues** in patients with GPA. The presence of C-ANCA has been associated with disease activity and rate of relapse.

GPA is an autoimmune disease where **genetic predisposition appears to play a critical role in the etiology**. Alpha-1 antitrypsin gene, cytotoxic T-lymphocyte antigen 4 gene, PTPN22\*620W gene, and DPB\*0401 gene have been all linked to GPA.

The main pathology of Goodpasture's disease is the presence of **autoantibodies that attack the alveoli and the basement membrane of the glomerulus**. These anti-GBM antibodies are also found in the blood of the patient. Anti-GBM antibodies leak from the endothelium of the glomerulus and interact with certain GBM glycoproteins.

This interaction activates glomerular infiltration of monocytes and polymorphonuclear leukocytes (PMNs). Fibrinogen from the damaged GBM leaks into the Bowman space, where it gets polymerized into fibrin. Eventually, **crescent formation ensues and the glomeruli are damaged by this mechanism**. A similar mechanism is believed to happen with the alveolar basement membrane in the lungs.

**Cigarette smoking, viral infections, and genetic predisposition are the main risk factors** for Goodpasture's disease. Polymorphisms in the Col4alpha3NC1 allele which is concerned with T-cell function have been linked to Goodpasture's disease.

Additionally, the human leukocyte antigen (HLA) DRB1\*1501 is also associated with an increased risk of anti-GBM disease. HLA-DR2 is also positive in 88% of patients with Goodpasture's syndrome. **HLA-DR2 is positive only in one-third of the general healthy population.**

## Clinical Presentation of Granulomatosis with Polyangiitis and Goodpasture's Syndrome

GPA might present with a history of recurrent infections in addition to a chronic history of constitutional symptoms. The **main constitutional symptoms of GPA are:**

- Fever
- Fatigue
- Weight loss
- Night sweats

Conjunctivitis, uveitis, episcleritis, and proptosis are also commonly seen in patients with GPA.

Chronic sinusitis is seen in two-thirds of GPA cases. Epistaxis is also a common finding of GPA and is found in 10% of the cases. **Saddle nose deformity due to the collapse of nasal support is commonly seen** in patients with GPA. Stridor because of tracheal or subglottic granulomatosis might be seen.

**The main pulmonary findings of GPA are:**

- Dyspnea
- Crackles
- Cough
- Hemoptysis
- Diffuse pulmonary infiltrates

Polyarticular symmetric joint pain can be seen. Arthritis is rarely seen in GPA. In **10% of the cases, the main presentation might be that of end-stage renal disease.**

Peripheral nervous system involvement typically occurs in two-thirds of the patients.

**Mononeuritis multiplex, sensorimotor polyneuropathy, and cranial nerve palsies are the main findings** seen in peripheral nervous system disease in patients with GPA. Lacunar infarctions due to small and medium-sized blood vessel disease of the central nervous system have also been described in a few patients.

**Also seen in patients with GPA are:**

- Pericarditis
- Myocarditis
- Endocarditis
- Conduction abnormalities
- Heart valvular disease

The **main presenting feature of Goodpasture's disease is hemoptysis.** Dyspnea, fatigue and cough are also seen.

## Overview:

| Constitutional  | Pulmonary   | Renal  |
|---|---|--|
| <ul style="list-style-type: none"><li>• Fever, fatigue, malaise</li><li>• Anorexia, weight loss</li></ul> | <ul style="list-style-type: none"><li>• Hemorrhage</li><li>• Cough, hematemesis</li><li>• Pulmonary nodules</li></ul> | <ul style="list-style-type: none"><li>• Hematuria</li><li>• Proteinuria</li><li>• Hypertension</li><li>• Renal failure</li></ul> |

**Hemoptysis usually happens one year before the onset of kidney disease.**

Anemia and pallor are more commonly seen in Goodpasture's disease. Pulmonary hemorrhage is the main feature of Goodpasture's disease and should be diagnosed as early as possible for proper treatment.

**Symptoms and signs of renal disease in Goodpasture's syndrome in children include hematuria and oliguria.** Edema can be seen in some patients. Hypertension is rarely seen in children with Goodpasture's disease-related kidney involvement.

## Diagnostic Workup for Granulomatosis with Polyangiitis and Goodpasture's Syndrome

Laboratory investigations in GPA might reveal elevated creatinine and blood urea nitrogen levels. **Normochromic normocytic anemia might be seen in half of the cases of GPA.** Erythrocyte sedimentation rate and C-reactive protein levels are elevated in 90% of the cases. Patients with kidney disease related to GPA typically have:

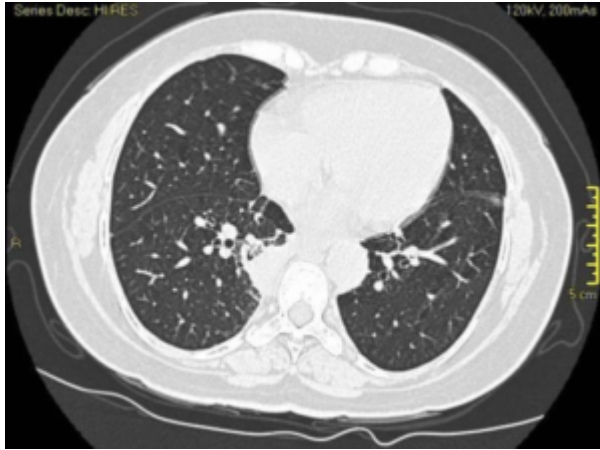
- Proteinuria
- Hematuria
- Red blood cell casts

**ANCs can be detected with serologic testing.** The available assays can detect C-ANCA, perinuclear P-ANCA, and atypical ANCA. The presence of C-ANCA against PR3 is most specific for GPA. C-ANCA is positive in approximately 90% of the cases of GPA. C-ANCA levels can be also used to predict relapse. A rising level is worrisome and it can mean that a relapse is coming soon.

### Different types of ANCA

| c-ANCA   | p-ANCA               |
|--|----------------------|
| IBD  | IBD                  |
| Primary sclerosing cholangitis   | Drug vasculitis      |
| Eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss) | Autoimmune hepatitis |
| Granulomatosis with polyangiitis (previously Wegener's)                  |                      |
| Cystic fibrosis  |                      |

Chest X-rays in GPA typically show multiple nodules and masses. Cavitation of the nodules is



[Image](#): "High resolution CT scan of the chest showing the lung nodules." by Pai S, Panda M. License: [CC BY 2.0](#)

seen in half of the cases. Diffuse alveolar hemorrhage can present as diffuse alveolar opacities. **High-resolution computed tomography (HRCT) can be used in the evaluation of the lungs** in a patient with GPA.

The typical findings on lung HRCT are consolidation, patchy and diffuse ground-glass opacities. Destructive sinusitis is commonly seen in GPA. Thin-section sinus CT scans are used to evaluate the sinuses in children with GPA.

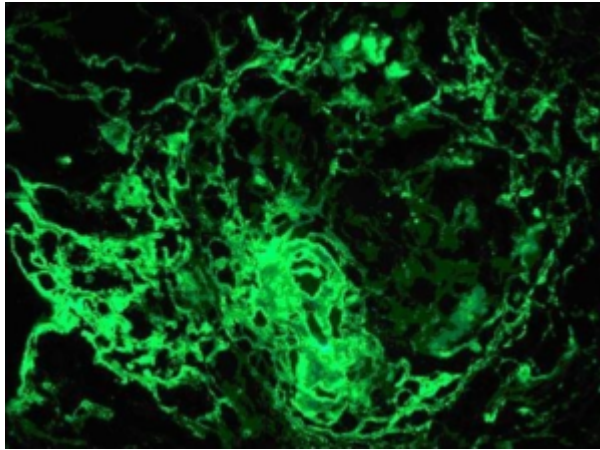
The diagnosis of GPA is confirmed with tissue biopsy from a site of active disease. The **mainly biopsied organs are the lungs and kidneys**. Tissue diagnosis is usually not needed as the clinical picture when combined with a positive C-ANCA result might be enough to make the diagnosis with high probability.

A lung biopsy can show parenchymal necrosis, vasculitis and granuloma formation. Kidney biopsy typically reveals segmental pauci-immune crescentic necrotizing glomerulonephritis in patients with GPA. **Leukocytoclastic vasculitis is the main finding of a skin biopsy in a patient with GPA.**

The diagnostic workup for Goodpasture's disease also starts with measuring ANCA levels in the serum. The presence of ANCA and anti-GBM antibodies in the serum of the patient is considered enough to make the diagnosis of Goodpasture's disease. **Patients with kidney disease typically have proteinuria.**

Microscopic hematuria and red blood cell casts are also found in patients with Goodpasture's disease. **Anemia is usually more severe in patients with Goodpasture's disease** compared to those with GPA. The erythrocyte sedimentation rate is normal or mildly elevated; another differentiating feature from GPA.

The presence of linear immunoglobulin G deposits along the glomerular capillary can be confirmed by immunofluorescence studies of renal biopsy.



**Image:** "Immunofluorescence findings of linear glomerular capillary wall positivity of 3 + intensity for IgG with 1-2+ C3, 3+ kappa and 2+ lambda support the diagnosis of anti GBM disease." by Patel D, Nivera N, Tunkel AR. License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Crescentic glomerulonephritis is also a common finding with Goodpasture’s disease.

Chest radiography is indicated in all patients suspected to have Goodpasture’s disease. The **main goal of chest radiography is to exclude pulmonary hemorrhage**. Patchy or diffuse lung infiltrates are the main radiological features of pulmonary hemorrhage.

Pulse oximetry is also indicated as hypoxemia is a common finding in patients with Goodpasture’s disease. A lung biopsy to confirm the diagnosis can be obtained with bronchoscopy and bronchoalveolar lavage.

## Management of Granulomatosis with Polyangiitis and Goodpasture’s Syndrome

GPA is mainly treated with corticosteroids and cytotoxic drugs. To **choose an appropriate treatment regimen in GPA, the disease needs to be graded**. The following table summarizes the grading of GPA per the European Vasculitis Study Group recommendations.

| Grade          | Description  |
|----------------|--|
| Localized      | <ul style="list-style-type: none"> <li>Upper or lower respiratory tract disease without any other organ involvement and without constitutional symptoms</li> </ul> |
| Early Systemic | <ul style="list-style-type: none"> <li>Involvement of any other organ other than the lungs, but without major organ damage</li> </ul>                              |
| Generalized    | <ul style="list-style-type: none"> <li>Renal or another organ considerable damage</li> <li>Serum creatinine level &lt; 5.6 mg/dL</li> </ul>                        |
| Severe         | <ul style="list-style-type: none"> <li>Renal or another organ considerable damage</li> <li>Serum creatinine level &gt; 5.6 mg/dL</li> </ul>                        |
| Refractory     | <ul style="list-style-type: none"> <li>Progressive GPA unresponsive to standard treatment with steroids and cyclophosphamide</li> </ul>                            |

Remission induction therapy of GPA mainly consists of cyclophosphamide plus corticosteroids, rituximab plus high-dose glucocorticoids, or glucocorticoids alone.

**Glucocorticoids alone are no longer recommended.** Patients with severe GPA or refractory GPA should undergo plasma exchange therapy. Localized GPA usually responds well to methotrexate.

Remission maintenance therapy mainly consists of:

- Azathioprine
- Methotrexate
- Rituximab
- Leflunomide

These therapies are typically used for one year and a half after remission.

The **treatment of Goodpasture's disease is largely dependent on plasma exchange therapy**. Plasma exchange therapy has been suggested to be performed for two weeks on a daily basis at the beginning of the treatment plan.

This approach should also be used in children, but the **duration of treatment should be lowered to 5 days instead of two weeks**. Cyclophosphamide use during this period is also recommended by some experts.

The risk of end-stage renal disease is higher in Goodpasture's disease compared to GPA. Patients with end-stage renal disease should be evaluated for the possibility of renal transplantation.

## References

[Pediatric Anti-GBM Disease \(Goodpasture Syndrome\)](#) via [emedicine.medscape.com](http://emedicine.medscape.com)

[Granulomatosis with Polyangiitis \(Wegener Granulomatosis\)](#) via [emedicine.medscape.com](http://emedicine.medscape.com)

[Wegener's Granulomatosis](#) via [hopkinsvasculitis.org](http://hopkinsvasculitis.org)

[Granulomatosis with polyangiitis](#) via [mayoclinic.org](http://mayoclinic.org)

[Goodpasture Syndrome](#) via [niddk.nih.gov](http://niddk.nih.gov)

**Legal Note:** Unless otherwise stated, all rights reserved by Lecturio GmbH. For further legal regulations see our [legal information page](#).