Churg-Strauss Syndrome: Etiology, Clinical Manifestations, and Treatment Strategies - A Review

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Abstract: Churg-Strauss Syndrome (CSS), or Eosinophilic Granulomatosis with Polyangiitis (EGPA), is a rare systemic vasculitis affecting small- to medium-sized blood vessels. It is characterized by asthma, eosinophilia, and multiorgan inflammation impacting the lungs, skin, nerves, and heart. While its exact cause remains unknown, genetic predisposition, environmental factors, and immune dysregulation are thought to play roles. Medicinal plants like *Curcuma longa, Echinacea purpurea*, and *Boswellia serrata*, known for their anti-inflammatory and immune-modulating properties, may offer supportive benefits. This review examines the causes and pathophysiology of CSS, emphasizing eosinophilic inflammation and immune dysfunction. It discusses traditional treatments such as corticosteroids and immunosuppressants, as well as emerging biologic therapies like anti-IL-5 monoclonal antibodies, particularly in refractory cases. The review also highlights the importance of early diagnosis and advances in biomarkers and imaging techniques for accurate detection.CSS arises from genetic, environmental, and immune factors. Early diagnosis and management are critical for improving patient outcomes, with future research focusing on refining diagnostics and exploring plant-based interventions.

Keywords: Churg-Strauss Syndrome, Eosinophilic Granulomatosis with Polyangiitis, Asthma, corticosteroids.

Introduction:

In 1951 Jacob Churg and Lotte Strauss, pathologists discovered Churg-Strauss Syndrome (CSS), also referred to as Eosinophilic Granulomatosis with Polyangiitis (EGPA). Churg-Strauss Syndrome is a complex type of systemic vasculitis (1). This condition primarily affects individuals who have a history of allergic diseases. CSS targets sized blood vessels, eosinophilia, and granulomatous inflammation, which is due to elevated levels of eosinophils in the blood. Due to the identification of these characteristics, CSS is now grouped into the larger category of antineutrophil cytoplasmic antibody (ANCA) associated with vasculitides. It is important to remember that only ANCA positives are 40% of CSS, suggesting a degree of variation in the pathogenesis of the disease (2).

CSS typically has three distinct phases: an initial prodromal phase characterized by asthma and allergic rhinitis; an eosinophilic characterized by eosinophilia in eosinophil infiltration of organs and peripheral blood; and a final vasculitic phase, where the systemic vasculitis damage in multiple organ systems. Lung involvement in patients suffering from asthma, pulmonary infiltrates, eosinophilic pneumonia, or exacerbations. But the CSS affects the skin, which leads to purpura or nodules; the peripheral nervous system, which can result in polyneuropathy. The heart is significant and can cause morbidity due to pericarditis, and myocarditis (3).

CSS involves multisystem and clinical heterogeneity is extremely challenging to detect and manage. CSS is rare and diagnoses are frequently delayed due to the overlapping of symptoms with other types of allergic disorders. This becomes problematic because untreated CSS can cause severe organ damage and increased mortality. Understanding the mechanisms of CSS can be useful for better therapy. However, early diagnosis will be essential for long-term prognosis and prevent organ damage (4).

This review aims to provide causes, clinical features, and therapeutic options for Chrug-Strauss syndrome. Additionally, it also highlights the current advances in the field, especially in the

development of novel therapeutic strategies that focus on specific targets of the CSS pathophysiology. This review explores the knowledge and management of potentially life-threatening illnesses.

Causes Churg-Strauss Syndrome:

Churg-Strauss Syndrome is a complex disease whose cause is unknown. However, CSS is widely caused by the combination of environmental stressors, immune system dysregulation, and genetic predisposition

Genetic Elements*:* Churg-Strauss Syndrome is developed significantly by the influence of genetic predisposition. Specific genetic polymorphism is a major cause of CSS and has been reported in several investigations. Polymorphism in the human leukocyte antigen (HLA) region has been linked to an increased incidence of CSS. HLA is responsible for the presentation of antigens to immune cells. Immune system reaction responses depend on the variations in the genes and lead to autoimmune diseases like CSS (5). Similarly, other genetic variations that lead to the generation of antineutrophil cytoplasmic antibodies (ANCA) may also contribute to the development of CSS.

Other genetic variations responsible for the alteration of the immune system have also been linked to Churg-Strauss Syndrome. Genes that are involved in coding interleukin-5 (IL-5) are associated with CSS. IL-5 is an important cytokine that supports the activation of eosinophils, which are essential to the CSS pathophysiology. ANCA is linked to the vasculitic phase of 40 % of CSS cases. This suggests genetic factors are responsible for the dysregulation of immune systems in CSS patients (6).

Environmental Triggers: The onset of CSS is believed to be caused by various environmental factors, based on the individuals with a genetic predisposition. Environmental factors such as drug reactions, infections, and allergens exposures lead to the development of CSS.

Drug Exposures: The use of certain drugs such as montelukast and corticosteroids, has been associated with Churg-Strauss Syndrome patients with asthma. The exact mechanism of cause is unclear, but montelukast (leukotriene receptor antagonists) and inhaled corticosteroids might cause an imbalance in the immune system resulting in Churg-Strauss Syndrome (7). Infections: Several infections such as viral infections caused by Parvovirus B19 or EBV (Epstein-Barr Virus) have been linked to the onset of CSS, due to their ability to stimulate the exaggerated immune response (8).

Allergens: Asthmatic patients exposed to various allergens such as pollen or dust mites have also been potentially leading to the CSS as a characteristic of eosinophilic inflammation. The interlink between CSS patients and allergen exposure gives a path that the disease may develop from an exaggerated immune response in genetically susceptible individuals (9).

Immune Dysregulation: Immune dysregulation is a hallmark of CSS and is central to its pathogenesis. The disease is characterized by the overproduction of eosinophils, a type of white blood cell involved in allergic reactions and parasitic infections. This eosinophilia is primarily driven by IL-5, which promotes the survival, activation, and recruitment of eosinophils to various tissues.

Eosinophilia*:* The persistent increase in eosinophil levels causes tissue infiltration, a process in which eosinophils discharge chemokines, cytokines, and toxic granules, that cause inflammation and destroy tissue. the multiple organs like skin, lungs, nerves, and heart are affected by this process which also contributes to the granulomatous inflammation and vasculitis observed in CSS (2).

Antineutrophile cytoplasmic antibodies and Autoimmunity: In 40 % of Eosinophilic Granulomatosis with Polyangiitis, perinuclear antineutrophile cytoplasmic antibodies (pANCA) are found and contribute to the vasculitic phase, which targets neutrophil and

monocyte components. According to Sable Fourtassou et al. (3), the presence of ANCA causes the wrong target by body cells and causes vascular damage and inflammation.

The interaction of immunological dysregulation, environmental triggers, and hereditary variables emphasizes the complexity of CSS and stresses the need for a multimodal strategy to address the illness.

Diagnosis of Churg-Strauss Syndrome:

A combination of clinical manifestation, imaging studies, laboratory tests, and histopathological examination are used for the diagnosis of CSS. A comprehensive evaluation is required to differentiate CSS from other forms of vasculitis and eosinophilic disorders.

The American College of Rheumatology (ACR) established diagnostic criteria for Churg-Strauss Syndrome (CSS), now referred to as Eosinophilic Granulomatosis with Polyangiitis (EGPA), that require the presence of at least four out of six clinical features. This system provides a sensitivity of 85% and a specificity of 99.7% for diagnosing the condition (10-12).

Asthma: Asthma is a hallmark of EGPA, often developing several years before the onset of vasculitis and progressively worsening over time. Patients may present with increased shortness of breath, wheezing, and chest tightness, which are common features of airway inflammation and hyperreactivity (10).

Eosinophilia: Elevated eosinophil levels (greater than 10% of total white blood cells) in the peripheral blood are a crucial diagnostic marker for EGPA. This eosinophilic inflammation contributes to tissue damage in various organs, including the lungs, heart, and gastrointestinal tract, and is central to the pathophysiology of the disease (10).

Neuropathy: EGPA frequently involves peripheral nerve damage, manifesting as mononeuropathy (affecting a single nerve) or polyneuropathy (involving multiple nerves). Symptoms include pain, numbness, and weakness in the extremities. Neuropathy in EGPA

results from vasculitis, which restricts blood flow to the nerves and leads to their dysfunction (10).

Pulmonary Infiltrates: Transient or migratory pulmonary infiltrates, which appear and disappear on imaging such as chest X-rays or CT scans, are indicative of EGPA. These infiltrates are related to eosinophilic inflammation within the lungs, causing respiratory symptoms like shortness of breath, coughing, and chest pain. The intermittent nature of these infiltrates is a diagnostic clue (10).

Paranasal Sinus: In Churg-Strauss Syndrome (CSS), also known as Eosinophilic Granulomatosis with Polyangiitis (EGPA), paranasal sinus abnormalities such as chronic sinusitis are common features. These abnormalities are typically driven by the underlying eosinophilic inflammation that characterizes the disease. Chronic sinusitis may manifest as prolonged nasal congestion, facial pain, nasal discharge, and headaches. Radiological imaging, such as CT scans, often reveals mucosal thickening and opacifications within the sinuses, which can be accompanied by nasal polyps in some patients. These symptoms are thought to result from the damage to the mucosal lining caused by the eosinophilic infiltration and inflammation typical of EGPA (2).

Biopsy: Although biopsy is not always necessary if other diagnostic criteria are strongly met, it remains the gold standard for confirming a diagnosis of CSS/EGPA. If performed, a biopsy typically targets organs showing clinical involvement, such as the skin, lungs, or peripheral nerves. The hallmark histopathological finding in CSS is vasculitis with eosinophilic infiltration. Specifically, a biopsy may reveal eosinophils in the tissue surrounding blood vessels (extravascular eosinophils), a characteristic feature of the disease (13).

Laboratory Tests in Churg-Strauss Syndrome (CSS)

Laboratory tests are crucial in diagnosing Churg-Strauss Syndrome (CSS), also known as Eosinophilic Granulomatosis with Polyangiitis (EGPA), by identifying key biomarkers that

indicate eosinophilic inflammation and immune dysregulation. These tests help differentiate CSS from other systemic vasculitides and allergic conditions.

Eosinophilia: Peripheral blood eosinophilia is a hallmark feature of CSS/EGPA and is central to the diagnosis. Eosinophil counts in affected individuals typically exceed 1,500 cells/μL (microliter of blood), although levels may reach even higher during disease flares. This elevated eosinophil count reflects eosinophilic infiltration in various tissues and organs, contributing to the characteristic symptoms such as asthma, neuropathy, and pulmonary involvement. The persistence of high eosinophil levels is considered a key diagnostic clue for CSS (10). The degree of eosinophilia is often monitored over time to assess disease activity and response to treatment (14).

Antineutrophil Cytoplasmic Antibody (ANCA) Positivity: Approximately 40% of CSS patients test positive for antineutrophil cytoplasmic antibodies (ANCA), particularly the perinuclear ANCA (p-ANCA) subtype, which targets myeloperoxidase (MPO). ANCA positivity is more commonly associated with patients who exhibit more severe vasculitic manifestations, such as neuropathy or glomerulonephritis. Studies suggest that ANCA-positive patients tend to have a more vasculitic presentation, while ANCA-negative patients are more likely to present with eosinophil-driven disease, including severe asthma and eosinophilic lung involvement (14). The presence of ANCA antibodies helps distinguish CSS/EGPA from other forms of vasculitis and guides treatment decisions, particularly in patients with renal involvement.

Elevated Serum IgE Levels: Serum immunoglobulin E (IgE) levels are frequently elevated in CSS/EGPA patients. The increase in IgE levels reflects the underlying allergic and eosinophilic immune response characteristic of CSS. Elevated IgE levels, combined with eosinophilia and a history of allergic diseases such as asthma and rhinitis, help differentiate CSS from other forms of systemic vasculitis, such as Granulomatosis with Polyangiitis (GPA) or Microscopic

Polyangiitis (MPA) (2). The degree of IgE elevation may also serve as a marker of disease activity, especially during disease flares.

Imaging Studies in CSS: Imaging studies are essential in assessing the extent of organ involvement, particularly in the lungs and sinuses, which are frequently affected in CSS. These imaging modalities provide insights into the extent of inflammation, tissue damage, and eosinophilic infiltration.

Chest X-rays and CT Scans: In patients with CSS, chest X-rays and CT scans are commonly used to detect pulmonary infiltrates, which are often transient or migratory. These infiltrates represent areas of eosinophilic inflammation in the lungs. Imaging may reveal patchy, nodular opacities, or ground-glass patterns that shift location over time, reflecting the intermittent nature of the eosinophilic lung involvement (11). These infiltrates often correspond to symptoms such as cough, shortness of breath, and pleuritic chest pain. Repeated imaging can track the migration of these pulmonary infiltrates, which is characteristic of eosinophilic lung disease in CSS (15). CT scans are more sensitive than chest X-rays and can provide a detailed assessment of parenchymal damage, fibrosis, and the presence of pleural effusion, which may occur in advanced stages of the disease. Radiological findings of pulmonary involvement, combined with clinical features, strongly suggest CSS/EGPA in the appropriate clinical context.

Sinus Imaging: Chronic sinusitis and other sinus abnormalities are common in CSS, reflecting the eosinophilic inflammation in the upper respiratory tract. CT scans of the sinuses are commonly used to evaluate the degree of mucosal thickening and detect abnormalities such as nasal polyps or sinus opacification. Sinus imaging may reveal diffuse mucosal thickening and air-fluid levels, indicating long-standing inflammation and obstruction of the normal drainage pathways (2). Chronic sinusitis is often an early feature of CSS and may precede other systemic manifestations, making it a useful diagnostic clue.

Sinus imaging, combined with clinical findings such as nasal polyps and asthma, helps distinguish CSS from other causes of chronic sinusitis, such as allergic rhinitis or chronic infectious sinusitis. Identifying sinus involvement early in the disease course can guide appropriate management, particularly in patients who may benefit from corticosteroids or immunosuppressive therapy to control inflammation**.**

Histopathological Findings: The granulomatous inflammation, eosinophilic infiltration, blood vessels, and vasculitis are the hallmarks of histological findings in CSS. The distinctive character is extravascular eosinophils within the tissue help to differentiate CSS from other vasculitic syndromes (7).

Site of Biopsy: Based on the clinical presentation the choice of biopsy depends. Skin lesions are frequently accessible for biopsy. In cases of lung biopsy, more invasive, in situations with neuropathy peripheral nerve biopsies are performed less commonly due to the possibility of consequences.

Treatment of Churg-Strauss Syndrome:

The treatment of Churg-Strauss Syndrome is based on the organs and severity of the disease. The main objective of the treatment is to control symptoms, avoid relapses, and induce remission. Because of the complexity of CSS, it is necessary to use immunosuppressive agents, biological treatments, and corticosteroids.

Corticosteroids: Systemic corticosteroids become very important for the treatment of CSS. These medications are useful in lowering inflammation and managing eosinophilia. Prednisone is the most commonly used corticosteroid, typically initiated at a high dose (e.g., 0.5–1 mg/kg/day) and then gradually tapered based on the patient's clinical response and side effects. Efficacy**:** Corticosteroids are effective in controlling symptoms related to vasculitis, asthma, and eosinophilia. Most patients achieve remission with corticosteroid therapy alone, especially in milder cases of CSS (2). The tapering of corticosteroids is individualized, often over months

to years, to minimize the risk of relapse while reducing the long-term side effects associated with steroid use, such as osteoporosis, diabetes, and hypertension (2).

Immunosuppressive Agents*:* For patients with severe or refractory disease or those at high risk of relapse, immunosuppressive agents are often added to corticosteroid therapy. These drugs are particularly important in cases with significant organ involvement, such as renal or cardiac disease.

Cyclophosphamide: This alkylating agent is frequently used in the induction phase of treatment for patients with severe vasculitis. It is highly effective but associated with significant toxicity, including an increased risk of infections and long-term malignancy. Cyclophosphamide is typically administered intravenously in monthly pulses or orally, depending on the clinical scenario.

Azathioprine and Methotrexate*:* These immunosuppressive agents are commonly used in the maintenance phase of treatment to prevent relapse after the induction of remission. Azathioprine and methotrexate have a more favourable side effect profile than cyclophosphamide and are suitable for long-term therapy.

Biologic Agents:

Recent advancements in the treatment of CSS have led to the use of biological agents that target specific components of the immune response. These therapies offer new options, particularly for patients with refractory disease or those who cannot tolerate conventional immunosuppressive therapy. Mepolizumab is an anti-IL-5 monoclonal antibody that has shown significant efficacy in reducing eosinophilia and controlling disease activity, especially in patients with severe or refractory asthma associated with CSS. It works by targeting IL-5, a key cytokine involved in the production and activation of eosinophils, thereby reducing eosinophilic inflammation (13). Ongoing research is exploring other biological agents, such as those targeting IL-4/IL-13 and IL-17 pathways, which are involved in the pathogenesis of CSS.

These therapies hold promise for further improving outcomes in CSS patients, particularly those with refractory or relapsing disease (15).

Treatment of Comorbid Conditions:

Managing comorbid conditions, particularly asthma and allergic symptoms, is crucial in the overall treatment strategy for CSS.

Asthma Management: Inhaled corticosteroids, leukotriene receptor antagonists, and bronchodilators are commonly used to control asthma symptoms in CSS patients. These medications help reduce airway inflammation and improve respiratory function (5).

Cardiovascular Monitoring: Regular monitoring for cardiovascular complications, such as myocarditis and heart failure, is essential, as cardiac involvement is a significant cause of morbidity and mortality in CSS. Appropriate management may include the use of heart failure medications, such as ACE inhibitors, beta-blockers, and diuretics, depending on the clinical scenario (7).

Monitoring and Long-term Management:

Long-term follow-up is critical in the management of CSS to monitor for disease relapse, treatment-related side effects, and the development of comorbidities.

Regular Monitoring: Regular assessment of eosinophil counts, ANCA titers, and organ function (e.g., renal, cardiac, and pulmonary) is recommended to detect early signs of relapse or treatment toxicity (7).

Adjusting Therapy: Treatment regimens may need to be adjusted based on the patient's response to therapy, side effects, and the presence of comorbidities. A multidisciplinary approach involving rheumatologists, pulmonologists, cardiologists, and other specialists is often required to provide comprehensive care.

Table 1. **Drugs used in Churg-Strauss Syndrome and its mechanism**

Drug	Mechanism of action	Reference
Azathioprine	An immunosuppressive agent that inhibits purine synthesis, leading to reduced proliferation of T and B lymphocytes	(10)
Prednisone	Glucocorticoid reduces inflammation by inhibiting multiple inflammatory pathways, including cytokine production, and immune cell activation	(10)
Cyclophosphamide	Alkylating agent that suppresses the immune system by cross-linking DNA, leading to reduced T and B cell activity	(10)
Methotrexate	Folate antagonist that inhibits DNA synthesis, leading to decreased lymphocyte proliferation and immune response	(10)
Mepolizumab	Monoclonal antibody targeting IL-5, which reduces eosinophil production and survival, thereby decreasing eosinophilic inflammation	(10)
Rituximab	Monoclonal antibody targeting CD20 on B cell, leading to B- cell depletion and reduced antibody production	(4)
Mycophenolate Mofetil	Inhibits inosine monophosphate dehydrogenase, leading To reduced proliferation of T and B cell	(5)

Plant used to manage Churg-Strauss Syndrome:

There is no well-established plant specifically used to treat Churg-Strauss Syndrome (CSS), also known as Eosinophilic Granulomatosis with Polyangiitis (EGPA), within the context of modern clinical practice. However, some plants are known for their anti-inflammatory and immunomodulatory properties, which theoretically could be of interest in the management of inflammatory or autoimmune conditions, though they are not clinically validated for CSS. Below is a summary of a few such plants, along with references:

1. Turmeric (*Curcuma longa*):

Figure 1. *Curcuma longs*

Curcuma longa, commonly known as turmeric, has long been recognized for its extensive therapeutic properties, particularly due to its active compound curcumin, which exhibits a broad spectrum of pharmacological activities (16, 17). In pharmacognosy, turmeric's bioactive potential is a subject of ongoing research, highlighting its role in managing inflammatory, oxidative, and microbial conditions (17).

This plant has been traditionally used in Ayurvedic medicine, and its modern applications continue to grow as new formulations aim to enhance curcumin's bioavailability (18). Curcumin has well-documented anti-inflammatory and antioxidant properties. It inhibits various molecules involved in inflammation, such as cytokines, nuclear factor-kappa B (NF-κB), and cyclooxygenase-2 (COX-2). While turmeric is used in some traditional medicine

systems to reduce inflammation, its role in treating autoimmune diseases like CSS has not been studied rigorously (19,20).

2. Echinacea (Echinacea spp.):

Figure 2. *Echinacea purpurea*

Echinacea, commonly known as coneflower, is a genus of herbaceous flowering plants in the daisy family, Asteraceae. Native to North America, *Echinacea* has been used for centuries by Indigenous peoples for its medicinal properties, particularly in treating infections and wounds (21). In modern herbal medicine, *Echinacea* is widely used as an immune system booster and is particularly popular for its potential to prevent and treat the common cold and other respiratory infections (22).

The most commonly used species in herbal medicine are *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida*. These species contain a variety of active compounds, including alkamides, polysaccharides, glycoproteins, and caffeic acid derivatives, which contribute to their immunomodulatory, anti-inflammatory, and antioxidant effects (23).

Echinacea is believed to stimulate the immune system by increasing the activity of white blood cells and enhancing the body's ability to fight off infections. It is also known for its ability to reduce the duration and severity of symptoms associated with colds and flu (24,25) Echinacea

is known for its immune-boosting properties. It can modulate cytokine production and enhance the activity of macrophages and natural killer cells. While Echinacea

is commonly used to prevent or treat upper respiratory infections, its immune-stimulating properties may not be suitable for autoimmune diseases, as it could potentially exacerbate conditions like CSS.

3. Boswellia (*Boswellia serrata*):

Figure 3. *Bowsellia serrata resin*

Boswellia serrata, commonly known as Indian frankincense, is a traditional anti-inflammatory agent widely used in Ayurvedic medicine. The resin, rich in boswellic acids, has been shown to inhibit the 5-lipoxygenase enzyme, which plays a crucial role in the inflammatory process (26). Due to these properties, Boswellia serrata is used to manage conditions such as osteoarthritis, rheumatoid arthritis, and inflammatory bowel disease, offering a natural alternative to NSAIDs with fewer gastrointestinal side effects (27,28). Additionally, it has shown potential benefits in asthma management by reducing inflammation and improving respiratory function (29). Boswellic acids exhibit anti-inflammatory effects by inhibiting 5-lipoxygenase, an enzyme involved in the synthesis of leukotrienes, which are mediators of inflammation. Boswellia is used in traditional medicine for conditions like arthritis, and some preliminary studies suggest it may help in reducing inflammation, but its efficacy in treating CSS is unknown.

Conclusion

In conclusion, Churg-Strauss Syndrome (CSS), or Eosinophilic Granulomatosis with Polyangiitis (EGPA), is a rare but complex vasculitis with a multifactorial etiology involving genetic, environmental, and immune system dysfunction. Early diagnosis and treatment are critical for preventing severe organ damage and improving patient outcomes. While corticosteroids and immunosuppressants remain the standard of care, emerging biologic therapies like anti-IL-5 monoclonal antibodies show promise, particularly in refractory cases. Additionally, medicinal plants such as Curcuma longa, Echinacea purpurea, and Boswellia serrata, with their anti-inflammatory and immune-modulating properties, may offer complementary benefits in managing the disease. Future research should focus on refining diagnostic methods, exploring novel treatments, and investigating the potential of these plant-based interventions.

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