

# Churg-Strauss Syndrome

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## Abstract

*Churg-Strauss syndrome (CSS) is a systemic disorder characterized by asthma, transient pulmonary infiltrates, hypereosinophilia, and systemic vasculitis. Eosinophilic vasculitis may involve multiple organ systems, including the lungs, heart, skin, gastrointestinal tract and nervous system. Thus allergy and angiitis are the two hallmarks of CSS. Conditions in the differential diagnosis of CSS include Wegener's granulomatosis (WG), drug reactions, bronchocentric granulomatosis, eosinophilic granuloma, fungal and parasitic infections, and malignancy. Onset typically occurs in patients aged from 15 to 70 years. A recent German population-based epidemiological study of a population of nearly 5 million people revealed an incidence of 1 per year per one million. Although CSS has long been considered as a rare disease, there has been a recent increase in case reports in association with different asthma therapies. CSS has been divided into 3 distinct phases, which may or may not be sequential. The prodromal phase is characterized by asthma with or without allergic rhinitis. The second phase is marked by peripheral blood eosinophilia and eosinophilic tissue infiltration producing a picture similar to simple pulmonary eosinophilia (Loeffler's syndrome), chronic eosinophilic pneumonia, or eosinophilic gastroenteritis. The third, vasculitic phase may involve any organ of these organs: lung, heart, peripheral nervous system, kidney, lymph nodes, muscle, and skin. Skin involvement occurs in more than two thirds of patients. Although the exact etiology of CSS is unknown, this syndrome is likely believed to represent an autoimmune process because of the prominence of allergic features and the presence of immune complexes, heightened T-cell immunity and altered humoral immunity, as shown by elevated immunoglobulin (Ig) E and rheumatoid factor. Treatment consists of glucocorticoid (GC)-monotherapy, data on outcome and effectivity is lacking on other immunosuppressive regimens such as cyclophosphamide (CP) or GC plus CP. Treatment with INF-alpha has been effective in patients refractory to GC plus CP.*

## Keywords

Systemic vasculitis, asthma, pulmonary infiltrates, hypereosinophilia, allergic angiitis, granulomatosis

### Disease name and synonyms

Allergic Angiitis and Granulomatosis  
 Allergic Granulomatosis and Angiitis  
 Eosinophilic Granulomatous Vasculitis  
 Churg-Strauss Vasculitis

### Definition

Churg-Strauss syndrome (CSS) is a systemic disorder characterized by asthma, transient pulmonary infiltrates, hypereosinophilia, and systemic vasculitis. Eosinophilic vasculitis may involve multiple organ systems, including the lungs, heart, skin, gastrointestinal tract and nervous system. The three main histological features found on the pathological examination of CSS cases are extravascular granulomas, tissue eosinophilia, and necrotizing vasculitis. Thus allergy and angiitis are the two hallmarks of CSS.

### History and Diagnostic Criteria

Churg and Strauss first described this syndrome in 1951 when they reviewed a number of autopsy cases that were previously classified as polyarteritis nodosa. These cases were atypical: they were associated with asthma and extravascular granulomas as well as systemic vasculitis. This disease is now known as "Allergic granulomatosis and angiitis" or "Churg-Strauss syndrome".

Although no universal agreement on CSS criteria has been reached so far, the most commonly used criteria are those developed by the American College of Rheumatology (ACR). The ACR criteria include both clinical and pathological features and classify CSS as the presence of four of the following six features: asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormality and eosinophilic vasculitis (table 1).

**Table 1: American college Of Rheumatology 1990: Classification criteria for Churg-Strauss syndrome**

<ul style="list-style-type: none"> <li>- Asthma</li> <li>- Eosinophilia &gt;10%</li> <li>- Pulmonary infiltrates</li> <li>- Mono-or poly neuropathy</li> <li>- Paranasal sinus abnormality</li> <li>- Extravascular eosinophils on biopsy</li> </ul> <p><b>A patient can be classify as CSS if at least 4 of these 6 criteria are met. In this case, sensitivity is 85% and specificity is 99.7%</b></p>
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### Differential diagnosis

Conditions in the differential diagnosis of CSS include [Wegener's granulomatosis](#) (WG), drug reactions, bronchocentric granulomatosis, eosinophilic granuloma, fungal and parasitic infections, and malignancy. Although each of these disorders may meet the ACR criteria for

CSS, the treatment algorithm differs significantly for each of them. Therefore, it is extremely important to obtain tissue when diagnosis is difficult to establish and before starting therapy.

**Table 2: Diseases associated with pulmonary infiltrates and eosinophilia in the differential diagnosis of Churg-Strauss Syndrome**

<p><u>Acute eosinophilic pneumonia</u></p> <p>Allergic bronchopulmonary aspergillosis (ABPA)</p> <p>Asthma</p> <p>Bronchocentric granulomatosis</p> <p><u>Chronic eosinophilic pneumonia</u></p> <p>Drug reactions</p> <p><u>Eosinophilic granuloma/histiocytosis X</u></p> <p>Bacterial, fungal, mycobacterial, and parasitic infections</p> <p>Malignancy</p> <p><u>Wegener's granulomatosis</u></p>
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In full-blown disease, CSS is easily differentiated from WG both by clinical and histological means. However cases sharing features of both diseases have been described. Therefore Schmitt *et al.* used an artificial neuronal network to further delineate the distinction between these disease entities based on clinical findings.

### Frequency

Onset typically occurs in patients aged from 15 to 70 years and the disease affects both males and females. The mean annual incidence in England is 2.4 per million inhabitants. The estimated prevalence of CSS in Norway is 1.3 per 100,000 inhabitants compared to 5.3 for WG. A recent German population-based epidemiological study of a population of nearly 5 million people revealed an incidence of 1 per year per one million compared to 8 for WG. In another German study, the period prevalence rate of CSS in 1994 was 7 per one million compared to 58 for WG.

Although CSS has long been considered as a rare disease, there has been a recent increase in case reports in association with different asthma therapies. This has raised the questions of how rare this disease truly is and whether incidence has indeed increased in association with various forms of asthma therapy. In particular, CSS in association with asthma therapy was first reported in 1998 in patients receiving zafirlukast, but there have since been several reports of the syndrome in association with both montelukast and panlukast, as well as with various inhaled corticosteroids.

Wechsler *et al* estimated that the incidence of CSS in association with leukotriene modifiers was approximately 60-cases/1,000,000 patients/year. In a retrospective analysis of prescription-event monitoring database of the Drug Safety Research Unit in Northampton, UK, Martin *et al* corroborated this estimate by looking

at CSS in patients receiving three asthma therapies (bambuterol, salmeterol, and nedocromil) and concluded that the period prevalence of CSS in this asthma population was 64 cases per million patient-year.

### Clinical description

CSS has been divided into 3 distinct phases, which may or may not be sequential (table 3). The prodromal phase is characterized by asthma with or without allergic rhinitis. The second phase is marked by peripheral blood eosinophilia and eosinophilic tissue infiltration producing a picture similar to simple pulmonary eosinophilia (Loeffler's syndrome), chronic eosinophilic pneumonia, or eosinophilic gastroenteritis. The third, vasculitic phase may involve any organ of these organs: lung, heart, peripheral nervous system, kidney, lymph nodes, muscle, and skin. Skin involvement occurs in more than two thirds of patients.

**Table 3: Clinical phases of Churg-Strauss Syndrome**

#### Prodromal phase

"Late-onset" allergic disease, early twenties  
See evidence of asthma (cough, wheezing, dyspnea)  
Allergic rhinitis, (nasal obstruction, chronic rhinitis, nasal polyposis)

#### Eosinophilic phase

Marked peripheral eosinophilia, eosinophilic tissue inflammation  
Typical organs involved include lungs, GI tract, and skin

#### Vasculitic phase

Constitutional symptoms (fever, myalgias, weight loss)  
Cardiac symptoms: principle cause of death (coronary vasculitis, congestive heart failure, endocarditis, pericarditis)  
Neurological symptoms (mononeuritis multiplex)  
Skin symptoms (subcutaneous skin nodules)  
Kidney disease

### Respiratory symptoms

The most common presenting manifestation of CSS is asthma, although as many as 2% of patients may develop airway symptoms after the onset of systemic vasculitis. Asthma often occurs in individuals who have no family history of atopy. It is severe and requires treatment with oral corticosteroids to control symptoms, which may lead to suppression of vasculitic symptoms. In addition the more common symptoms of cough, dyspnea, sinusitis, and allergic rhinitis, alveolar hemorrhage and hemoptysis may also occur.

### Neurological symptoms

Neurological involvement is the second most common manifestation and occurs in approximately 78% of patients. Mononeuritis multiplex most commonly involves the peroneal nerve but may involve the ulnar, radial, internal

popliteal and occasionally, cranial nerve. Isolated weakness, such as foot drop, is a common manifestation. Polyneuropathy often develops in the absence of treatment and may be symmetric or asymmetric. Cerebral hemorrhage and infarction may also occur and are important causes of death. Despite treatment, neurological sequelae do not often completely resolve.

### Dermatologic symptoms

Approximately half of CSS patients develop dermatological manifestations. These include palpable purpura, skin nodules, urticarial rashes, and livedo. They usually present on the limb surfaces but can affect any part of the body.

### Cardiovascular symptoms

The heart is a primary target organ in CSS and its involvement often portends a worse prognosis. Granulomas, vasculitis and widespread myocardial damage may be found on biopsy or at autopsy, and cardiomyopathy and heart failure may be seen in up to half of all patients but are often at least partially reversible. Acute pericarditis, constrictive pericarditis, myocardial infarction, and other electrocardiographic changes may occur.

### Gastrointestinal symptoms

Gastrointestinal symptoms are common in CSS. They often consist in an eosinophilic gastroenteritis characterized by abdominal pain, diarrhea, gastrointestinal bleeding, and colitis. Ischemic bowel, pancreatitis, and cholecystitis also have been reported in association with CSS and usually portend a worse prognosis.

### Renal symptoms

Renal involvement may include proteinuria, glomerulonephritis, interstitial nephritis, and (but seldom) renal failure. Renal biopsy may show focal segmental glomerulonephritis, crescents or other necrotizing features. Systemic hypertension is also common.

### Other symptoms

Constitutional symptoms are very common in CSS and include weight loss of > 10% of the body weight, fever (commonly higher than 38° for 2 weeks), and diffuse myalgias and migratory polyarthralgias. Myositis may be present with evidence of vasculitis on muscle biopsy.

### Etiology

Although the exact etiology of CSS is unknown, this syndrome is likely believed to represent an autoimmune process because of the prominence of allergic features and the presence of immune complexes, heightened T-cell immunity and

altered humoral immunity, as shown by elevated immunoglobulin (Ig) E and rheumatoid factor.

Observations of CSS in cases with parasitic disease (e.g. ascaris, trichinosis) suggest that in many cases hyperresponsiveness to an antigenic stimulus, such as a parasite or allergen, underlies the syndrome.

In 1998, Wechsler *et al.* reported 8 patients who developed CSS when oral corticosteroids were tapered after treatment with zafirlukast, an antagonist of the cysteinyl leukotriene receptor type 1 (CysLT1). Further reports described a clinical syndrome resembling CSS in association with the other CysLT1-receptor antagonists (montelukast, pranlukast). Evaluating all the available data on this topic, the causal relationship between leukotriene antagonists and CSS is far from clear. However, it was noted that, in many of these case reports, CSS was diagnosed following reduction in the dose of systemic glucocorticosteroids (GC), thus suggesting that the reduced dose of GC was the factor that precipitated the “unmasking” of the vasculitic process. Churg *et al.* (1995) described cases of CSS that developed in the context of GC withdrawal. This theory is further supported by a report of 5 cases of CSS with severe steroid-dependent asthma in whom inhaled corticosteroids allowed systemic GC withdrawal. An alternative explanation is that CSS is a hypersensitivity reaction to this class of drugs, a theory supported by a number of reports of patients who developed CSS without ever receiving GC before the introduction of CysLT1-receptor antagonists. Since the annual incidence of CSS in patients taking zafirlukast appears to be near the upper limit for the population of asthmatics in general, it is quite possible that the risk of developing CSS under zafirlukast is comparable to that associated with other anti-asthma-drugs. So, the population-based incidence of CSS in the general population has to be compared with its incidence in the population of asthmatics.

### Pathology

Whereas immune complex deposition was initially favored as the mechanism of vascular injury in CSS (immune-complex vasculitis), we know from more recent studies that most cases show no evidence of immune protein deposition in the vascular wall. In their series, Hattori *et al.* (1999) clearly demonstrated that IgG and C3d deposits are seen only occasionally in epineuronal vessel walls of the sural nerve (pauci immune vasculitis).

Peen *et al.* (2000) recently demonstrated the presence of major basic protein in muscle fibers undergoing necrosis in a small bowel biopsy specimen from CSS and discussed the role of

other eosinophilic granule proteins such as ECP (eosinophil cationic protein) and eosinophil-derived neurotoxin (EDN) in the underlying pathological process.

These findings are in keeping with the high levels of serum ECP and the excretion of urinary EDN in patients with CSS and reflect ongoing in vivo eosinophil degranulation in active disease due to cell activation. In a case report these authors mention that serial measurements of plasma IL-4, IL-5, and IL-13, serum ECP and blood and urine EDN clearly revealed that IL-13 and EDN, but not IL-4, IL-5, or ECP, paralleled the elevated non-specific inflammatory markers. These results contrast with the findings of others concerning ECP and IL-5. In another case report, IL-5 and ECP were found to be elevated in active CSS and to decline after treatment with interferon  $\alpha$  (IFN- $\alpha$ ) in a therapy (GC plus cyclophosphamide (CP))-resistant situation. Investigating the cytokine production pattern of T-cell lines (TCL) in CSS, Kiene *et al.* (2001) found significant differences between CSS and WG with respect to phenotype and cytokine profiles, as well as between CSS and healthy controls (HC). Classification of the TCL according to phenotype and IFN- $\alpha$ : IL-4 ratio revealed a polarization toward a CD4+, Th0 pattern in patients with CSS, compared with a CD8+, Th1 pattern in patients with WG, and a CD4+, Th1 pattern in HC. Moreover, a significant increase in IL-4 and IL-13 production was found in TCL of patients with CSS versus TCL derived from patients with another granulomatous disease (e.g. WG). In addition, there was a positive correlation between IL-4 production and the eosinophil count in CSS, further substantiating the hypothesis that CSS is a Th2-mediated disease, which in turn activates eosinophils and thus mediates the tissue damage.

In T cells the CD95/CD95 ligand system is a major pathway of apoptotic cell death and thus essential for prevention of lymphoproliferative disorders and autoimmunity. Soluble CD95 was identified as a survival factor for eosinophils which rescued them from apoptosis in the absence of growth factors in vitro. Given the role of eosinophils as effector cells in CSS, these findings suggest that soluble CD95 may be mechanistically involved in the disease. The same authors found recurrent oligoclonal T-cell expansions in 5 out of 7 CSS patients; all using a Vb-gene from the Vb21 family associated with similar CDR3 motifs, indicating the predominance of T-cell clones with a similar specificity in these patients. This contrasts markedly with the clonal proliferation of type 2 helper T cells in hypereosinophilic syndrome.

These abnormal T cell clones produce IL5 in idiopathic eosinophilia.

### Diagnostic methods

Systemic eosinophilia is the hallmark laboratory finding in patients with CSS and reflects the likely pathogenic role-played eosinophils. Eosinophilia greater than 10% is one of the defining features of this pathology and may be as high as 75% of the peripheral blood cell count. It is present at time of diagnosis in more than 80% of patients but may respond rapidly (often within 24 hours) to initiation of systemic corticoid therapy. Even in the absence of systemic vasculitis eosinophilia may be present. The clinical value of ANCA (antineutrophil cytoplasmic antibodies) in CSS is questionable. Since CSS is relatively rare "orphan disease", many reports are based on a small number of patients. Summing-up the available data, Eustace *et al.* (1999) showed that, among 82 CSS patients tested for ANCA, 52% (!) were negative; 23 patients were pANCA positive and 12 patients cANCA positive in the indirect immunofluorescence test. In most of the pANCA-positive patients the antibody was directed against myeloperoxidase (MPO-ANCA). Serum markers of lymphocyte activation and endothelial damage, such as soluble thrombomodulin and soluble IL2 receptor, correlate with disease activity; however, the serum marker of eosinophil activation, eosinophil cationic protein (ECP), is also known to closely parallel clinical disease activity. Hurst *et al.* (2000) confirmed this fact, they were able to demonstrate that ECP serum levels can predict a relapse of CSS. Eosinophil active cytokines were analyzed in the serum of 5 patients by Tsukadaira *et al.* (1999). They found elevated IL-5 (and TNF- $\alpha$ ) in the serum and bronchoalveolar lavage fluid. In addition, newly expressed surface antigens such as CD25 and CD69 were observed on peripheral blood eosinophils, showing that these cells are activated. Circulating cytokines and soluble CD23, CD26 and CD30 were analyzed by Schönermark *et al.* (2000): only IL10 levels were significantly elevated in CSS.

### Radiographic features

Radiographic chest abnormalities are extremely common in CSS and consist of bilateral nonsegmental, patchy infiltrates that often migrate and that may be interstitial or alveolar in appearance. Reticulonodular and nodular disease without cavitations can be seen, as well as pleural effusions and hilar adenopathy. The most common thin-section computed tomographic (CT) findings include bilateral ground-glass opacity and air-space consolidation

that is predominantly subpleural and surrounded by the ground-glass opacity. Other CT findings include bronchial wall thickening, hyperinflation, interlobular septal thickening, lymph node enlargement, and pericardial and pleural effusions. Angiography is often used for diagnosis and may show signs of vasculitis in the coronary and peripheral vessels and the central nervous system.

### Treatment

The use of cytotoxic agents and cyclosporine in the treatment of autoimmune diseases was reviewed following a Clinical Staff Conference held in 1997 at the National Institutes of Health, USA. Concerning the treatment of CSS it was stated that GC-monotherapy is the classic regimen and that the current data are insufficient to issue specific recommendations. The decision to use cytotoxic therapy should be made on a case-to-case basis depending on disease severity (e.g. cardiac involvement or severe polyneuropathy), response (resistance) to GC-therapy, and potential drug toxicity.

The French Vasculitis Study Group recently reported on the long-term follow-up of polyarteritis nodosa, microscopic polyangiitis, and CSS. Although this analysis of 4 prospective trials comprising a total of 278 patients has been criticized for including patients with different disease entities, some of its findings appear to be acceptable. First, CSS patients treated with GC plus CP had significantly prolonged survival in the group with more severe disease (5 factor score >2). Second, only patients treated with GC alone had uncontrolled disease. Third, CP was associated however with a greater frequency of side effects. In more recent series, the same authors describe CSS as being less severe than other vasculitides and to respond to orally administered GC. Moreover, long-term prognosis was not as poor as in the first series of cases. In a recent study of 96 patients, the actuarial survival at 6 ½ years was 72%.

As described above, CSS is thought to be a TH2-mediated disease in which activated eosinophils appear to be the major effector cells. The expression of IFN- $\alpha$  receptor has been demonstrated on eosinophils and T cells, and ligation of the receptor inhibits the expression of eosinophil-activating cytokines on T cells and the release of cytotoxic mediators of eosinophils, such as ECP or EDN. The benefit of IFN- $\alpha$  treatment in CSS patients resistant to GC plus CP appears to be plausible. In the future however the targeting of cytokines, e.g. with antibodies against IL5 as is done in asthma, may improve our treatment protocols.

### Unresolved questions

Although eosinophils are believed to play a central role in the pathogenesis of CSS, the etiology remains unknown.

Reports of CSS cases in association with the use of leukotrienes modifiers and inhaled corticosteroids have increased, but no causative role for these agents in the pathogenesis of CSS has been firmly established.

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