

# Sjögren's syndrome

**Author: Doctor Menelaos N. Manoussakis<sup>1</sup>**

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<sup>1</sup>Department of Pathophysiology, School of Medicine, National University of Athens, 75 Mikras Asias str., 11527 Athens, Greece. [menman@med.uoa.gr](mailto:menman@med.uoa.gr)

[Abstract](#)

[Keywords](#)

[Disease name and synonyms](#)

[Diagnosis Criteria/Definition](#)

[Differential Diagnosis](#)

[Prevalence](#)

[Clinical Description](#)

[Management including treatment](#)

[Etiology](#)

[Diagnostic methods](#)

[Unresolved questions](#)

[References](#)

## Abstract

*Sjögren's syndrome (SS) is a chronic autoimmune disorder. It is characterized by dysfunction and destruction of the exocrine glands associated with lymphocytic infiltrates and immunological hyperreactivity. Salivary and lacrimal glands are the most affected, thus leading to mouth and eye dryness. The disorder can occur alone (it is then known as "primary-SS") or in association with another autoimmune disease (it is then known as "secondary-SS"). Prevalence of primary-SS in the general population has been estimated to be around 1 to 3%. Although patients of all ages and of both sexes may be affected, this disorder mostly affects women (9:1 female to male ratio) in their fourth or fifth decade of life. In the majority of patients, SS has an indolent or slowly progressive course with disease confined in exocrine glands. Mild rheumatic complaints have also been reported. At presentation or during the course of the disease, almost one third of the primary-SS patients experiences a more generalized disease, which does not usually evolve to the failure of the affected organ. However, stringent follow-up should be instituted in patients with adverse prognosis predictors such as purpura, low C4-complement levels or mixed monoclonal cryoglobulins. Risk of developing lymphoma and mortality are higher in these patients. To date, the management of patients has primarily aimed to provide symptomatic relief to lessen mucosal dryness-induced damage and to early recognize and treat disease complications.*

## Keywords

Sjögren's syndrome, autoimmune epithelitis, autoimmune exocrinopathy, autoimmune rheumatic diseases, exocrine glands, epithelial cells, primary Sjögren's syndrome, secondary Sjögren's syndrome, lymphoma, autoantibodies.

## Disease name and synonyms

Sjögren's syndrome;(SS)  
Sjögren-Gougerot's syndrome;  
Mickulitz' syndrome;  
autoimmune exocrinopathy;  
autoimmune epithelitis;

Sicca syndrome.

## Diagnosis Criteria/Definition

No single symptom, sign or test is pathognomonic for SS (1). However, diagnosis is usually readily achieved by gathering information obtained from the clinical, histopathologic and

serologic assessment of patients. A set of diagnostic and classification criteria for the appraisal of the SS sicca manifestations have been determined (2). These include the affirmation of subjective complaints about oral and/or eye dryness, the objective evidence of salivary gland and/or ocular involvement, as well as of autoimmune reactivity, namely the presence of lymphocytic infiltrative lesions in the salivary glands (sialadenitis) and of serum autoantibodies against Ro(SSA) and La(SSB). Recently, occurrence of sialadenitis and presence of serum anti-Ro(SSA)/La(SSB) autoantibodies were introduced as compulsory classification criteria by the American-European Consensus Group (Table-1) (3).

**Table 1. The revised international classification criteria for Sjögren's syndrome**

**I. Ocular symptoms**

A positive response to at least one of the three following questions:

Have you had daily, persistent, troublesome dry eyes for more than three months?

Have you had recurrent sensation of sand or gravel in the eyes?

Do you use tear substitutes more than three times a day?

**II. Oral symptoms**

A positive response to at least one of the three following questions:

Have you had a daily feeling of dry mouth for more than three months?

Have you had recurrent or persistent swollen salivary gland as an adult?

Do you frequently drink liquids to aid in swallowing dry food?

**III. Ocular signs**

Objective evidence of ocular involvement is defined as a positive result in at least one of the following two tests:

Schirmer's I test, performed without anesthesia (< 5 mm in 5 minutes)

Rose-Bengal score or another ocular dye score (> 4 according to van Bijsterveld's scoring system)

**IV. Histopathology**

Presence of focal lymphocytic sialadenitis in minor salivary glands (obtained through normal-appearing mucosa), evaluated by an expert histopathologist with a focus score >1, defined as a number of lymphocytic foci which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes per 4 mm<sup>2</sup> of glandular tissue.

**V. Salivary gland involvement**

Objective evidence of salivary gland involvement is defined as a positive result in at least one of the following three tests:

Unstimulated salivary flow (< 1,5 ml in 15 min)

Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts.

Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

**VI. Autoantibodies**

Presence in the serum of the following autoantibodies: antibodies to Ro(SSA) or La(SSB) or both.

**Revised rules for classification**

For patients without any potentially associated disease the presence of any four of the six items is indicative of primary SS. For patients with a potentially associated disease (for instance another connective tissue disease) item 1 or item 2 plus any two from items 3, 4, 5 is indicative of secondary SS.

Exclusion criteria : pre-existing lymphoma, acquired immunodeficiency disease (AIDS), sarcoidosis, graft-versus-host disease, sialoadenosis, use of anti-depressant and anti-hypertensive drugs, neuroleptics, parasympatholytic drugs.

Test should be excluded from the criteria or not considered indicative for a diagnosis of SS in elderly subjects (older than 60 years).

**Differential Diagnosis**

Various acute or chronic medical conditions may simulate SS. These include adverse effects of drugs, infection, tumor, metabolic disorders and irradiation. In particular, sarcoidosis, lipoproteinemia (types-II, -IV and -V), chronic graft-versus-host disease, lymphoma, amyloidosis and infection by hepatitis C virus (HCV) or human immunodeficiency virus (HIV) might be misdiagnosed as SS (Table-2). In the elderly, mucosal dryness is frequently an age-related process characterized by degeneration and liposis of the exocrine glands.

**Table 2. Differential diagnosis of idiopathic primary SS from the SS-like disorder which is associated with infection by HIV or HCV viruses, or sarcoidosis.**

	Primary SS	HIV infection with sicca syndrome	HCV infection with sicca syndrome	Sarcoidosis
<b>Age</b>	Middle-age	Young	All ages	Middle-age
<b>Sex predilection</b>	Female	Male	No difference	No difference
<b>Anti-Ro(SSA) and anti-La(SSB) autoantibodies</b>	Frequently present	Absent	Absent	Absent
<b>Predominant T-cell type in lymphoid infiltrates</b>	CD4	CD8	CD4	Granuloma
<b>Diagnostic viral serologic test</b>	None	HIV tests	HCV tests	None
<b>HLA-association</b>	DR3, DRw53, DQA1*0501	HLA-DR5	Unknown	Unknown

**Prevalence**

Sjögren syndrome is a homogeneous disease that occurs worldwide with similar prevalence. The disorder mostly affects women (9:1 female to male ratio) in their fourth or fifth decade of life.

This predominance of SS in women seems to be related to the immunoregulatory properties of the sex hormones (20). However, patients of both sexes and all ages may be affected. Prevalence of primary-SS in the general population has been estimated to be around 1 to 3% (4,5), whereas secondary-SS has been observed in approximately 10-20% of patients with rheumatoid arthritis, systemic lupus erythematosus (SLE) and scleroderma (1). It is estimated that Sjögren syndrome is the second most common rheumatologic disorder, behind only SLE.

## Clinical Description

### **Glandular Features**

Chronic dryness of the mouth (xerostomia) and/or the eyes (keratoconjunctivitis sicca) due to diminished secretion of the saliva and tears is characteristic of the disorder (1). Moistening glands in the nose, the pharynx, the tracheobronchial tree, the skin and the stomach may be also affected. Troubles in chewing and swallowing, sore mouth and recurrent dental caries are common. The tongue is typically smooth with fissures and atrophy of the filiform papillae. Edentulous patients report very poor comfort with conventional dentures, however implant-retained prostheses are very well tolerated. Enlargement of the major salivary gland occurs in 25-66% of the primary-SS patients, but is uncommon in patients with secondary-SS. Bacterial infection or salivary gland tumor should always be suspected in unilateral salivary gland enlargement, even in patients with established diagnosis of SS. Chronic eye dryness leads to persistent irritation and to destruction of the corneal and bulbar conjunctival epithelium (keratoconjunctivitis sicca). Sandy or burning sensation is a complaint frequently reported and patients may be unable to tolerate smoke, air drafts or light.

### **Systemic manifestations**

Approximately half of the patients with primary-SS show evidence of extraglandular involvement, however, these systemic manifestations are often mild (1). Easy fatigue and low-grade fever are more frequent in patients with clinically significant extraglandular disease.

### **Musculoskeletal**

Most patients suffer from fatigue, whereas evidence of fibromyalgia is found in 12-30% of the patients. Arthralgia, myalgia and morning stiffness are very frequent. Non-erosive arthritis as well as a rheumatoid arthritis-like symmetric

polyarthritis may also occur. Despite myalgia and easy fatigue, frank myositis is unusual.

### **Respiratory tract**

In patients with primary-SS, involvement of respiratory system is frequent, however it is usually of limited clinical significance. Dry cough (due to xerotrachea or bronchitis sicca) is very common. Approximately half of the patients present with evidence of interstitial-like disease in plain chest radiography. High resolution computerized tomography often reveals bronchial or peribronchial thickening, usually associated with the presence of bronchiolar lymphoid infiltrates and follicular bronchiolitis. Lung nodules or hilar and/or mediastinal lymphadenopathy should always raise suspicion for lymphoma development.

### **Gastrointestinal tract and hepatobiliary system**

The dryness of the pharynx and oesophagus may produce dysphagia. Chronic atrophic gastritis and lymphocytic infiltrates of gastric mucosa may be observed, largely reminiscent of those in minor salivary glands. Liver involvement in primary-SS patients is rare (5%) and subclinical. By contrast, sicca manifestations are found in 50-80% of the patients with primary biliary cirrhosis. Small bowel biopsy reveals the occurrence of celiac-like disease in approximately 15% of the primary-SS patients.

### **Urinary tract**

Approximately one third of the SS patients present with evidence of distal renal tubular acidosis (type-I), which is usually subclinical. However, these patients can present with hypokalemic muscular weakness, recurrent renal colici which can lead to nephrocalcinosis if they are not treated. In a series of 471 primary-SS patients followed-up for 10 years, approximately 4% of the patients had clinically important renal disease manifested by interstitial nephritis or glomerulonephritis (6). Interstitial nephritis is found early in the disease course and is benign. On the contrary, immune complex glomerulonephritis (membranoproliferative or mesangial proliferative) is associated with cryoglobulinemia and hypocomplementemia and can lead to chronic renal insufficiency (6). Frequent micturition and suprapubic pain may imply interstitial cystitis often associated with lymphocytic infiltrative lesions.

### **Vasculature and skin**

Raynaud's phenomenon is found in more than 35% of the patients. Nailfold capillaroscopy often reveals scleroderma-like lesions in primary-SS patients with anti-centromere antibodies. Small-

vessel vascular inflammatory disease has been described in 20-30% of the primary-SS patients. Vasculitis of the skin is mostly observed, presenting with palpable purpuric or petechial lesions. Recurrent urticaria and annular erythema of the face and trunk may also be found. Systemic necrotizing vasculitis with visceral involvement affecting kidney, lung and gastrointestinal tract may occur. However, it is rare.

#### *Neuroendocrine and psychiatric system*

Entrapment syndromes, peripheral sensory or sensory-motor polyneuropathy and/or mononeuritis multiplex may occur. Hemiparesis, seizures, cerebellar defects and transverse myelopathy have been described in primary-SS patients, but this has not been confirmed. Evidence of autonomic dysfunction is found in certain patients with primary-SS, possibly mediated by antagonistic anti-M3 muscarinic receptor autoantibodies. Anxiety, depressed mood and personality disorders are frequently observed and may be associated with altered perception of emotional stress and/or dysregulated stress responses. Hypoactivity of hypothalamic-pituitary-adrenal axis has been demonstrated.

#### *Other manifestations*

Anti-thyroid antibodies and abnormal thyroid-hormone stimulation tests are common, but clinically overt autoimmune thyroiditis is not frequent. In a recent study, no significant difference has been observed in the prevalence of autoimmune and non-autoimmune thyroid disease between SS patients and controls (7). Sensorineural hearing loss is reported to occur in 20-45% of the SS patients. Fertility, parity and sexual activity are not affected apparently, whereas insufficient vaginal lubrication causing dyspareunia appears to be correlated with atrophic vaginitis and perivascular infiltration. Elevated erythrocyte sedimentation rate is detected in approximately 70% of the patients.

#### **Lymphoma development**

In primary-SS, predisposition for development of malignant non-Hodgkin's lymphoma (MNHL), which usually occurs later in the course of the disease, is well established (1). Whether secondary-SS also predisposes to lymphoma remains unclear. In primary-SS, lymphoma has been estimated to occur in approximately 4-6% of the patients followed-up for about 8 years. This frequency is considerably higher than that of rheumatoid arthritis (RA), where in the absence of immunosuppressive treatment, lymphoma occurs in approximately 1% of the patients. The

major risk factors for lymphomatous transformation in SS patients include persistent unilateral or bilateral parotid gland enlargement, splenomegaly and lymphadenopathy, as well as type II mixed monoclonal cryoglobulinemia. Various histologic subtypes of MNHL have been described, including follicle center lymphoma, lymphoplasmacytoid lymphoma, diffuse, large B-cell lymphoma, and mucosa-associated lymphoid tissue (MALT) lymphoma. According to a recent multi-center study of 33 primary-SS patients with MNHL, low-grade marginal-zone B-cell lymphoma (a term, which includes MALT and monocytoid B-cell lymphomas) was the predominant type (8). In most cases, the patients had good clinical performance status. Extranodal localization is very frequent and involves the salivary glands in approximately 55% of total lymphoma cases. The survival of these patients is closely associated with the histological grade of lymphoma; high- and intermediate- grade lymphomas have the worst prognosis, whereas low-grade lymphoma in SS patients may either remain stable for several years, or show temporary spontaneous regression or transform to a high-grade form. Patients at high risk of MNHL should be followed regularly. When this transformation occurs, treatment decisions rely on the stage and the grade of lymphoma.

#### **Secondary Sjögren's syndrome**

Features of SS may occur in almost every autoimmune rheumatic disease, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, primary biliary cirrhosis and mixed connective tissue disease (1). In some respects, sicca syndrome(s) that occur(s) in the context of distinct rheumatic diseases may take different forms. Sicca complaints are common (20%) in RA patients; however, clinically significant SS is found in only 5% of all the patients. Keratoconjunctivitis sicca is the main sicca manifestation, whereas xerostomia and salivary gland enlargement are quite uncommon. In addition, autoantibodies against Ro(SSA) and La(SSB), as well as distinct HLA haplotypes which typically characterize primary-SS, are rather uncommon in RA with secondary-SS. By contrast, patients with primary-SS and those with SS associated with SLE may present with similar clinical manifestations, *i.e.* arthralgias, rash, peripheral neuropathy and glomerulonephritis. Almost 20% of the patients with systemic sclerosis present with oral or ocular dryness often due to extensive fibrosis of the exocrine glands. By contrast, sicca manifestations associated with frank lymphocytic infiltrative

lesions are extremely common (60%) in patients with limited scleroderma.

### **Clinical course**

The initial presentation of the disorder at diagnosis essentially determines its outcome (9). In the vast majority of patients, the glandular sicca features and serologic profile remain unchanged through the disease course (9,10). This is apparently the case for most systemic extraglandular manifestations, except for the development of lymphoma and glomerulonephritis which are usually late events. Occurrence of palpable purpura, low C4-complement levels and mixed monoclonal cryoglobulins are adverse prognostic factors (9). The overall mortality of primary-SS is not different from that of general population (11). However, mortality is higher in patients with adverse predictors (9).

### **Biological findings**

Polyclonal B-cell hyperreactivity is one of the most prominent immunological features of SS and manifests itself by profound hypergammaglobulinemia, circulating immune complexes and multiple autoantibodies directed against both organ and non-organ specific autoantigens (1). Rheumatoid factors (RF), anti-nuclear antibodies (ANA), anti-histone and anti-single-stranded DNA antibodies are found in notably high levels and quite frequently (over 70% of the cases). By standard gel precipitation methods, antibodies to Ro(SSA) and La(SSB) are found in 40-60% and 25-40%, respectively, of primary-SS patients. Mothers with these autoantibodies are at a relatively increased risk of giving birth to children with congenital complete heart block. Recently, the cytoskeletal protein alpha-fodrin has been proposed as a candidate autoantigen in primary-SS, based on the antibody and T-cell reactivities found in patients.

Oligoclonal B-cell expansions in the form of monoclonal light chains or immunoglobulins in the serum and urine are found in 80-100% of patients with systemic involvement, compared to approximately 25-40% of patients with only glandular disease (1). In addition, approximately one third of primary-SS patients exhibit high serum levels of mixed polyclonal/monoclonal cryoglobulins (type II), which usually contain an IgMk-monoclonal RF. Signs of *in situ* lymphomatous transformation are frequently noted at the lymphoepithelial lesions of SS patients, whereas in the majority of patients with overt lymphoma, neoplastic tissue is located in the salivary glands.

## **Management including treatment**

### **General measures**

No clinical trial has shown the efficacy of any drug in altering the course of the disease yet. Patients follow-up and treatment aim to provide symptomatic relief to lessen mucosal dryness-induced damage and to early recognize and treat disease complications (12). The decision for systemic therapeutic intervention remains largely empirical and is primarily reserved for severe extraglandular disease. Since no or hardly any clinical benefit has been observed and due to potential side effects, administration of immunosuppressive agents is not recommended for the every-day treatment of SS. Aggressive treatment with cytotoxic drugs, such as cyclophosphamide, should be reserved for life-threatening systemic manifestations such as necrotizing vasculitis. Recently, the oral administration of a low-dose natural human interferon-alpha has been reported to provide relief for sicca symptoms and to improve saliva flow. When acute relief of symptomatology is needed, the patient may benefit of plasmapheresis. Infliximab (anti tumor necrosis factor-alfa antibodies) has shown some usefulness in the treatment of extraglandular symptoms and peripheral nervous system manifestations. This agent might be considered when all other treatment modalities have failed given the presumed importance of tumour necrosis factor in the pathogenesis of Sjogren's syndrome (21). Use of localised gene transfer has been proposed to develop new treatment strategies for the salivary component of Sjogren's syndrome (22).

### **Dryness of mucosae**

The main objectives of treatment are to prevent keratoconjunctivitis sicca and dental disease to stimulate residual saliva and tear secretion and to treat infection when required. Protective measures against windy or dry climates, dust and smoke should be taken. Diuretics, antihypertensive drugs, antidepressants and antihistamines should be used with caution. Eye lubricants are used for keratoconjunctivitis sicca as often as necessary. Patients with residual glandular function may benefit significantly from the administration of the muscarinic M3 receptor agonists, pilocarpine and cevimeline (13,14). Infection should always be suspected when sudden aggravation of symptoms and/or excessive mucus production occurs. Corticosteroid-containing ophthalmic solutions should be avoided. Dental treatment with fluoride delays damage of teeth surfaces. Propionic acid gels or other vaginal lubricants may be used to

treat vaginal dryness and dyspareunia. In menopause, the administration of conjugated estrogens as vaginal cream or oral tablets may be helpful.

### **Salivary gland enlargement**

Swelling of parotid and submandibular glands is frequent and most often regresses spontaneously without treatment. Local application of moist heat may be helpful, as well as non-steroidal anti-inflammatory drugs. A tender gland with permanent enlargement should always raise suspicion for bacterial infection. Corticosteroids may be used with caution, as they may exacerbate infection. Performing tissue biopsy should be always considered to exclude lymphoma.

### **Musculoskeletal manifestations**

Non-steroidal anti-inflammatory drugs or hydroxychloroquine are frequently used for the treatment of arthralgia, myalgia and constitutional symptoms. Treatment with hydroxychloroquine has been reported to improve features of immunological hyperreactivity in primary-SS patients, however, double-blind controlled studies are lacking. For persistent arthritis, methotrexate may be used, as recommended for RA.

### **Renal involvement**

To avoid the development of nephrocalcinosis, patients with overt distal renal tubular acidosis should receive sodium or potassium bicarbonate orally at a dose sufficient to diminish acidosis, hypokalemia and hypercalciuria. Membranoproliferative glomerulonephritis is initially treated with prednisone. In refractory cases, monthly intravenous pulses of cyclophosphamide should be administered.

### **Pulmonary involvement**

For severe dry cough from desiccation of the tracheobronchial tree, hydration, humidifiers at bedtime and muscarinic M3 receptor agonists should be tried. Yearly pulmonary function tests are recommended.

### **Vascular manifestations**

For patients with Raynaud's phenomenon, exposure to cold, emotional stress and smoking should be avoided. Nifedipine given orally may help to reduce frequency and severity of vasospasm. Leukocytoclastic vasculitis is a common problem that does not require specific therapy. Systemic necrotizing vasculitis can be treated with prednisone and intravenous cyclophosphamide pulses, as mentioned above, as well as plasmapheresis.

### **Malignant lymphoma**

Treatment of malignant lymphoma in SS patients is based on its histological type, location and extent, as for lymphoid neoplasias in general. For low-grade lymphomas of the exocrine glands a watchful attitude is recommended.

### **Etiology**

The etiology of SS remains largely obscure. A viral etiology has long been suspected for the induction of SS, however, no definite conclusion has been drawn (1). Although genetic influences are thought to be responsible for pathogenesis, no such single factor has been identified. Studies from different countries and ethnic groups have revealed associations with various HLA-DR alleles (DRB1 genes), including DR3, DR5, DRw11 and DRw53. The association of primary-SS with DQA1\*0501, DQB1\*0201 and DQB1\*0301 alleles appears to cross ethnic barriers. On the basis of focal lymphoid infiltrative lesions and prominent autoantibody responses, SS exocrinopathy is considered as an autoimmune disorder. The autoantibody responses may contribute significantly to glandular epithelial dysfunction of patients. Recently, it has been shown that antagonistic anti-M3 muscarinic receptor autoantibodies are capable of having inhibitory influence on parasympathetic neurotransmission (15). Increasing body of evidence suggests that the affected glandular epithelia may have a role in the induction and maintenance of chronic immune activation in SS patients (16). Cultured non-neoplastic salivary gland epithelial cell lines derived from SS patients have been shown to manifest increased spontaneous expression of various activation- and immune response-associated molecules, which possibly indicates the operation of intrinsic activation processes in SS epithelia (17,18). Epithelial cells of salivary gland are functionally competent to stimulate the growth of activated T cells, suggesting the potential of these cells to participate in antigen-mediated activation and proliferation of T lymphocytes (19).

### **Diagnostic methods**

#### **Oral and ocular components**

Overt SS is associated with severely reduced production of unstimulated whole saliva (less than 1,5 ml in 15 min). Digital subtraction sialography or scintigraphy (99mTc-sodium pertechnate) can be used with high diagnostic accuracy for SS. Wetting of a paper strip (placed at the lower lid) of less than 5-mm/5 min is a strong indication of diminished tear secretion (Schirmer's test). Staining of damaged corneal

and conjunctival epithelia by Rose Bengal dye is a more specific assay for keratoconjunctivitis sicca than Schirmer's test in elderly subjects.

### **Histological assessment**

The presence of focal or diffuse sialadenitis is one of the most consistent features of SS. Typical lesions consist of multiple focal mononuclear aggregates that replace glandular structures. A focus score >1 is considered to be an indicator of SS, with "focus score" defined as the number of lymphocytic foci which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes per 4 mm<sup>2</sup> of glandular tissue.

### **Serological tests**

Strongly positive tests for ANA, RF and antibodies to Ro(SSA) and La(SSB) antigens corroborate the diagnosis. In particular, the identification of serum autoantibodies to Ro(SSA) or La(SSB) proteins in a patient with sicca complaints is a strong clue for the diagnosis of the disorder. Monitoring of the serum levels of the above-mentioned autoantibodies is not helpful for the following-up or the prognosis of the patients.

### **Unresolved questions**

To determine the origin of chronic and persistent activation of immune system.

To elucidate the role of immunologic, immunogenetic and neuroendocrine factors in the pathogenesis of the disease.

To find a specific immunological intervention to alleviate disease

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