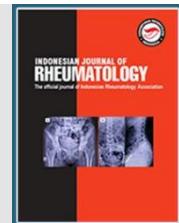




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## Indonesian Rheumatology Association (IRA) Recommendations for Diagnosis and Management of Sjogren's Syndrome

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### ABSTRACT

**Background.** Sjogren's syndrome (SS) is a systemic autoimmune disease that affects exocrine glands. Dealing with SS is challenging due to the low level of awareness and knowledge about SS, as well as the difficulty in diagnosing and treating the disease. Diagnosing SS requires many supporting examinations from many medical specialties. Therefore, these recommendations were developed to serve as a guide for health practitioners in diagnosing and treating SS. **Methods.** Six selected rheumatologists from the Indonesian Rheumatologist Association (IRA) formulated the recommendations based on key questions formed by a steering committee from IRA. These recommendation materials were taken from several online databases such as PubMed, Science Direct, and Google Scholar. Level of evidence and grades of recommendation were then assigned, and every member of the panelist team will assign a score for level of agreement.

**Results.** The panel generated a total of 19 recommendations discussing the diagnosis, pharmacological and non-pharmacological therapy, and prognosis for SS. **Conclusion.** These recommendations can be used to help clinicians correctly diagnose and choose the most suitable therapy for SS patients. All recommendation statements were created with the consideration of Indonesia's clinical setting, facility, and drug availability.

### 1. Introduction

Sjogren's syndrome (SS) is a chronic systemic rheumatic disease characterized by lymphocyte infiltration in exocrine glands, especially the salivary and lacrimal glands, causing gradual loss of function and dryness in the mouth and eyes.<sup>1,2</sup> The disease often affects individuals aged between 45 to 55 years

old, and is more prevalent in women, with the women-to-men ratio being 9:1.<sup>2,3</sup> The reported incidence of SS ranged from 0.1 to 3 cases per 1000 population.<sup>2</sup> Some SS patients also suffered from rheumatoid arthritis or other connective tissue diseases, including lupus.<sup>3</sup> Male SS patients were more likely to have malignancy together with SS and had increased

mortality rate compared to female SS patients.<sup>4</sup>

SS can occur in a previously healthy patient, which is then called primary Sjogren's syndrome (pSS).<sup>5</sup> SS can also occur simultaneously in a patient with other systemic autoimmune diseases, such as systemic lupus erythematosus (15-36%), rheumatoid arthritis (20-32%), and systemic sclerosis (11-24%).<sup>5</sup> In these cases, the disease is called secondary Sjogren's syndrome (sSS).<sup>5</sup> In rarer cases, SS may also occur in patients with multiple sclerosis, autoimmune hepatitis, and thyroiditis.<sup>6</sup>

At present, there is a lack of data regarding the epidemiology of Sjogren Syndrome in Indonesia. This recommendation was developed to serve as a guidance for the diagnosis and treatment of SS in Indonesia, raising the awareness of physicians, and facilitate early diagnosis of SS.

## 2. Methods

The recommendation team was assembled by The Indonesian Rheumatologist Association (IRA). The team consisted of 6 rheumatologists tasked with formulating key questions for diagnosis, therapy, and monitoring of SS. Additionally, there was also a team of supervisors (steering committee) consisting of 6 core members from IRA. The panelist team consisted of 51 rheumatologists from various branches of IRA and institutions in Indonesia, with at least five years of working experience as a rheumatologist. Each member of the panelist team gave an independent opinion regarding the level and strength of recommendation that was issued by the recommendation team. No delegation from the pharmacy industry was involved in the process of composing this recommendation.

A total of 9 key questions were formed to formulate the recommendations for diagnosing and managing SS in Indonesia:

1. What are the clinical manifestations of SS?
2. What diagnostic examinations are needed to

diagnose SS?

3. What are the classification criteria that can be used to diagnose SS?
4. What are the differential diagnoses of SS?
5. Are there specific instruments available to monitor disease activity in SS?
6. What are the general treatments for SS patients?
7. What are the systemic pharmacologic treatments for SS patients?
8. What are the glandular pharmacologic treatments for SS patients?
9. How is the prognosis of SS patients?

Literature searching was conducted through PubMed, Science Direct, Google Scholar, and other databases, using these keywords: Sjogren's syndrome, diagnosis, therapy, and monitoring. The literature was limited to meta-analyses, systematic reviews, clinical trials, randomized controlled trials (RCTs), and observational studies published in English. The literature was also limited to studies published within 2011 to 2021.

Subsequently, recommendations were formulated based on the 9 key questions above. The recommendation team then assigned the level of evidence (LoE) and grades of recommendation (GoR) based on the criteria listed in Table 1.7. The recommendations were then reviewed by the steering committee. In the final step, the panelist team members were asked to assign a score of 0-10 for each recommendation, to determine the level of agreement (LoA). A score of 0 means complete disagreement and 10 means complete agreement. The panelist member would be asked for comments should a score below 8 was issued. Each recommendation with an average score below 8 were then rediscussed by the recommendation team to be revised and then reassessed for determining the LoA from the panelist team.

Table 1. Level of Evidence and Grades of Recommendations

Level of evidence (LoE)		Grades of recommendation (GoR)	
I	High quality meta-analysis or systematic review of RCTs, or individual RCTs with low risk of bias	A	Strong recommendation: referring to level I studies
II	High quality systematic review of observational studies (case control or cohort), or individual observational studies	B	Moderate recommendation: referring to level II studies or extrapolation of level I studies
III	Non-analytic studies (case report or case series)	C	Weak recommendation: referring to level III studies or extrapolation of level II studies
IV	Non-analytic low quality studies (case report or case series)	D	Consensus recommendation: expert opinion or based on limited evidence

### 3. Results

Based on the discussion, 19 recommendations were agreed by the recommendation team, steering

committee, and the panelist team. Summary of these recommendations can be seen in Table 2.

Table 2. Summary of Recommendations for Diagnosis and Management of Sjogren's Syndrome

No	Recommendation	LoE	GoR	LoA
1	Anamnesis and complete physical examination, especially related to sicca symptoms, are crucial in diagnosing SS	II	B	9.6
2	Specific supporting diagnostic test, such as the anti SS-A/Ro test, is needed to help diagnose SS	II	B	9.5
3	SS classification criteria from ACR/EULAR 2016 can be used to help establish SS diagnosis while considering the inclusion and exclusion criteria.	II	B	9.5
4	Excluding differential diagnoses is needed to confirm the diagnosis of SS	III	C	9.3
5	Disease activity monitoring in SS can be done using ESSDAI	II	B	9.2
6	SS management is conducted using multidisciplinary approach	N/A	N/A	9.6
7	SS therapy includes local and systemic therapies, which are given according to the involved organ manifestations	N/A	N/A	9.6
8	SS patients should be educated regarding the disease and any risk factor that may aggravate the disease, including avoidance of certain drugs	I-IV	A-D	9.6
9	Regular, stepwise, and proportional exercise is recommended for SS patients experiencing fatigue	II	B	9.3
10	Systemic therapy in SS should be adjusted to the degree of severity and involvement of specific organ based on ESSDAI definition	III	C	9.2
11	Glucocorticoids should be used with the lowest possible dose in the shortest duration to control active systemic disease in SS. They are not considered as first line drugs	III	C	9.5
12	Immunosuppressive agents are mainly used as adjuvants to reduce glucocorticoids usage in SS	III	C	9.5
13	Biologic agent therapy can be considered in severe and refractory systemic SS	I	B	9.3
14	Dry eye therapy in SS consists of local and systemic therapy, which are chosen based on the severity of the disease	IV	C	9.5
15	Dry mouth therapy in SS is chosen based on the severity of the disease	I-IV	B-D	9.5
16	Salivary gland edema in SS can be treated with short-term oral prednisolone or intramuscular methylprednisolone in acute inflammation, and gland massage in chronic inflammation	IV	D	9.2
17	Non-hormonal vaginal moisturizer, with or without topical estrogen, is recommended for SS patients with vaginal dryness	I	A	9.4
18	Organ specific therapy approach for specific organ manifestations (glandular, articular, skin, pulmonary, renal, peripheral neuropathy, central nervous system, hematological) in SS includes the use of glucocorticoids, immunosuppressive agents, biologic agents, and combination therapy	IV	D	9.5
19	SS prognostic factors are assessed from disease activity, extra-glandular involvement, low complement levels, the presence of cryoglobulinemia, and other comorbidities	II	B	9.1

### 3. Discussion

#### **Recommendation 1: Anamnesis and complete physical examination, especially related to sicca symptoms, are crucial in diagnosing SS**

Clinical manifestations of SS are often dominated by sicca symptoms which are caused by glandular involvement. SS may also be accompanied by fatigue, musculoskeletal pain, and systemic manifestation. Sicca symptoms are specific hallmarks of SS, which

can manifest in many organs. About 94% of pSS patients experience ocular and oral dryness at the onset of diagnosis, and around 30% of these patients experience unilateral or bilateral parotid gland enlargement.<sup>8,9</sup> In general, SS clinical manifestations can be classified into exocrine gland manifestation and extra-glandular manifestation. These clinical manifestations can be seen in Table 3.

Table 3. Clinical Manifestation of Sjogren's Syndrome<sup>10-22</sup>

Organ	Clinical manifestation
Exocrine gland manifestation	
Mouth	Xerostomia (proven with hyposalivation), dysphagia, dental caries, dysgeusia, oral candidiasis
Eye	Keratoconjunctivitis sicca, corneal damage, uveitis, scleritis, and optical neuritis
Salivary gland	Parotid, submandibular, and other salivary gland edema
Genitourinary	Dyspareunia, bacterial and <i>Candida</i> infection, sexual dysfunction, decreased sexual activity and pleasure
Extra-glandular manifestation	
Musculoskeletal	Arthritis, fibromyalgia, myalgia
Skin	Xerosis, purpura, Raynaud phenomenon, cutaneous vasculitis, annular erythema, angular cheilitis
Lung	Airway disease, interstitial lung disease, xerotrachea
Cardiovascular	Hypertension, increased cardiovascular disease risk
Gastrointestinal, liver	Dysphagia, gastroesophageal reflux, nausea, vomiting, chronic diarrhea, constipation, primary biliary cirrhosis, autoimmune hepatitis, sclerosing cholangitis
Renal	Tubulointerstitial nephritis, renal tubular acidosis
Neurological	Peripheral: sensory/sensorimotor axonal polyneuropathy, sensory neuropathy and ganglionopathy, radiculopathy, multiplex mononeuritis Central: cognitive dysfunction, transverse myelitis, paralysis, meningitis, seizure, headache, optical neuritis, encephalopathy, and multiple-sclerosis-like demyelination
Hematological	Cytopenia, hypergammaglobulinemia, hypogammaglobulinemia, monoclonal gammopathy, cryoglobulinemia, and increased autoantibody titer

Dry eye syndrome is not exclusively caused by SS, it can occur in other diseases as well.<sup>23,24</sup> Dry eyes in SS are caused by aqueous deficiency, increased evaporation, or both.<sup>24-28</sup> Ocular involvement in SS can manifest as dry eyes, corneal melting, uveitis, scleritis, retinal vasculitis, and optical neuritis.<sup>29</sup> Most patients with dry eyes complain of watery eyes, burning sensation in the eyes, "foreign body sensation", itchiness, photophobia, blurry vision, redness, mucous discharge, increased blinking rate, and eye fatigue.<sup>25,30,31</sup> In order to accurately assess the condition of ocular surface, several screening tools can be used, such as OSDI (ocular surface disease index) and DEQ-5 (dry eye questionnaire 5).<sup>25,30,31</sup> Several objective examinations to assess the function of tear

gland may also be needed, including<sup>24,26,27</sup>: (1) Tear break up time, to assess tear film stability. (2) Corneal or ocular surface staining (OSS), to assess ocular surface using fluorescein, rose bengal, or lissamine green. (3) Schirmer test or phenol red thread, to assess tear film secretion. (4) Osmolarity test, to assess tear film composition

#### **Recommendation 2: Specific supporting diagnostic test, such as the anti SS-A/Ro test, is needed to help diagnose SS**

Several autoantibodies and increase in serum polyclonal immunoglobulin titer are often found in SS patients.<sup>6,26</sup> Erythrocyte sedimentation rate (ESR) also often increases in accordance with the increase of

gamma globulin. Autoantibodies that may be found in SS include anti SS-A/Ro (40%), anti SS-B/La (26%), ANA (74%), and RF (38%).<sup>28</sup> Hematological abnormalities that can be found are anemia (20%), leukopenia (16%), thrombocytopenia (13%), and hypergammaglobulinemia (80%).<sup>6,26</sup> Other laboratory parameters can also be used to assess risk factors of lymphoma in pSS patients, such as cryoglobulinemia, lymphopenia (especially from low CD4 T cells), hypocomplementemia, increased serum BAFF, and the presence of monoclonal component in the serum or urine.<sup>32,33</sup> Supporting eye examinations that can help in confirming SS diagnosis are Schirmer test, tear break-up time, and ocular surface test using fluorescein, rose bengal, or lissamine green.<sup>34-39</sup>

About 10-20% pSS patients may experience interstitial lung disease (ILD), therefore, conventional chest X-ray and/or CT scan or lung biopsy can be performed to confirm the diagnosis in patients with lung disturbance symptoms.<sup>40</sup> The abnormalities that may be found in lung CT scan are interstitial pneumonia, centrilobular abnormalities, and lymphoproliferative disease appearance.<sup>41</sup> Lung biopsy may also be needed to determine the phenotype of ILD, with non-specific interstitial pneumonia being the most common phenotype to be found in pSS patients with ILD (45%).<sup>26</sup> Kidney function test is also required, as 24% of pSS patients may suffer from

chronic kidney disease, most commonly interstitial nephritis.<sup>42,43</sup>

**Recommendation 3: SS classification criteria from ACR/EULAR 2016 can be used to help establish SS diagnosis while considering the inclusion and exclusion criteria**

The latest SS classification criteria was created and validated by American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) in 2016. The new criteria were more sensitive and could even classify patients without or with minimal sicca symptoms. The sensitivity was 87.4%, while the specificity was 95.4%. The ACR/EULAR 2016 classification criteria can be seen in Table 4. Labia minor salivary gland biopsy was added to the criteria because the procedure was relatively easy, and it could predict extra-glandular manifestation and also its progression into non-Hodgkin lymphoma. The specific histopathological finding was exocrine gland focal infiltration by lymphocytes (focal lymphocytic sialadenitis / FLS), with focus score of  $\geq 1$  per 4 mm<sup>2</sup>. Glandular involvement in SS can be assessed properly with salivary gland ultrasonography (SGUS), magnetic resonance imaging (MRI), salivary gland scintigraphy, and sialography.<sup>2,26,44</sup>

Table 4. SS ACR/EULAR 2016 classification criteria<sup>26,45</sup>

Criteria	Point
Focal lymphocytic sialadenitis of labial salivary gland, with focus score of $\geq 1$ per 4 mm <sup>2</sup>	3
Positive anti-SS-A/Ro	3
Eye staining score $\geq 5$ (or van Bijsterveld score $\geq 4$ ) in at least one eye	1
Schirmer test $\leq 5$ mm / 5 minutes, in at least one eye	1
Unstimulated salivary flow rate $\leq 0.1$ ml/minute	1
<ul style="list-style-type: none"> <li>• Inclusion criteria: individual with at least 1 dry eye symptom or dry mouth or ESSDAI <math>\geq 1</math></li> <li>• Exclusion criteria: previous history of head-neck radiation, active hepatitis C infection (confirmed by PCR), AIDS, sarcoidosis, amyloidosis, graft-versus-host disease, and IgG4-related disease</li> <li>• Patients are classified as SS if they have a score of <math>\geq 4</math> out of the five listed criteria</li> </ul>	

#### **Recommendation 4: Excluding differential diagnoses is needed to confirm the diagnosis of SS**

An understanding of the potential differential diagnoses of SS is essential to rule out other non-autoimmune etiologies which may also involve experts from other specialties. The differential diagnosis of SS includes other diseases that can cause sicca symptoms and salivary or lacrimal gland enlargement, and these differential diagnoses can be excluded based on the disease history, physical examinations, and evidence of systemic autoimmunity.<sup>46</sup>

#### **Recommendation 5: Disease activity monitoring in SS can be done using ESSDAI**

EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) is a clinical index used to measure systemic disease activity in pSS patients. This clinical index was developed in 2009. ESSDAI can also be used to compare therapy outcomes in SS.<sup>8,47,48</sup> ESSDAI consists of 12 domains, which shows systemic disease activity of several organs and laboratory test. The index includes several domains such as skin, joint, respiratory, renal, musculoskeletal, central, and peripheral nervous system.<sup>47</sup> Every domain is divided into 3-4 grades, based on the degree of activity (0: no activity; 1: low disease activity; 2: moderate disease activity; 3: high disease activity), and each domain has different score based on the degree.<sup>47</sup> The final index score is the sum of each score in each domain, which can range from 0 to 123. The final disease activity is classified into 3 levels: low (<5 points), moderate (5-13 points), and high (>13 points).<sup>48</sup>

#### **Recommendation 6: SS management is conducted using multidisciplinary approach**

Assessment and management of SS patients require multidisciplinary approach to exclude other non-autoimmune etiologies, to evaluate the degree of multiple organs involvement, and to tailor treatment plans based on individual clinical and biological manifestations of the disease.<sup>46</sup> The team coordinator

should be a doctor; a rheumatologist is much more preferred, who usually collaborates with primary care physicians, ophthalmologists, and oral medicine specialists.<sup>10</sup>

#### **Recommendation 7: SS therapy includes local and systemic therapies, which are given according to the involved organ manifestation**

Chronic SS often requires routine long-term therapy. Therefore, therapy with minimal side effects is preferred, or at least, treatment with tolerable and reversible side effects. Several systematic reviews support the use of daily topical therapy to reduce dryness symptoms and increase HRQoL (health-related quality of life) significantly without prominent side effects.<sup>49-51</sup> Topical or local therapy should be initiated after objective confirmation of gland dysfunction.<sup>26</sup>

Systemic disease is the main prognostic factor in SS, which is associated with irreversible autoimmune-mediated organ dysfunction. The use of immunomodulators or systemic immunosuppressive agents (glucocorticoids, anti-malaria, immunosuppressive agents, intravenous immunoglobulin, and biologic agent) should be restricted to patients with active systemic disease. However, it should be noted that systemic immunosuppressive agents should only be used after detailed evaluation and severity assessment of each organ, as not all patients with active systemic disease require systemic therapy.<sup>26</sup>

#### **Recommendation 8: SS patients should be educated regarding the disease and any risk factor that may aggravate the disease, including avoidance of certain drugs**

Education of SS patients is very important because it can influence the patients' condition, therapy outcomes, and the prognosis. The summary of education components that should be given is explained in Table 5.

Table 5. Summary of Education Components for SS Patients

General Education about SS (IV/D)
Patients should be explained about the etiology, course of disease, management, and prognosis about SS.
Diet Modification (I/B)
SS patients with dry eye manifestation should be given omega-3 fatty acid supplementation. <sup>24</sup>
Avoiding dryness-inducing drugs (II/B)
<ul style="list-style-type: none"> <li>- Anti-hypertension: clonidine, diuretics, prazosin, propranolol, reserpine</li> <li>- Antidepressant and psychotropics: amitriptyline, nortriptyline, amoxapine, trimipramine, clomipramine, desipramine, imipramine, diazepam, nitrazepam, doxepin, phenelzine, tranylcypromine, phenothiazine</li> <li>- Antiarrhythmics: amiodarone, disopyramide, mexiletine</li> <li>- Parkinson's disease drugs: benzotropine, biperiden, procyclidine, trihexyphenidyl</li> <li>- Anti-ulcer agent: atropine-like agents, metoclopramide</li> <li>- Muscle spasm drugs: cyclobenzaprine</li> <li>- Decongestant: ephedrine, pseudoephedrine</li> <li>- Antihistamine</li> <li>- Anesthetic agent: enflurane, halothane, nitrous oxide</li> <li>- Hormonal therapy: estrogen replacement therapy, androgen antagonist</li> </ul>
Modification of environmental factors that may induce dry eyes (IV/C) or oral dryness (III/C)
Environmental humidity is an important factor that can induce dry eyes. Tobacco smoke can decrease humidity and cause eye tear film evaporation; therefore, smoking should be avoided by SS patients. In severe SS, the use of goggles can be considered. SS patients with dry eyes should avoid the use of air conditioner.
Dry eyes treatment
<ul style="list-style-type: none"> <li>- Maintain optimal lid hygiene and compress using warm water (IV/C)<sup>24</sup></li> <li>- Consult an ophthalmologist every 3 months at the beginning of therapy, and continue consulting every 6 months (IV/D)<sup>52-56</sup></li> </ul>
Oral dryness treatment
<ul style="list-style-type: none"> <li>- Maintain good oral hygiene (IV/D)<sup>57</sup></li> <li>- Avoid consuming foods or drinks other than mineral water between meals, an hour before sleep, and the whole night (IV/D)<sup>58</sup></li> <li>- Conduct a routine examination to an oral medicine specialist<sup>59</sup></li> <li>- Avoid food containing acid or sugar (IV/D)<sup>60</sup></li> <li>- Maintain good oral humidity (IV/D)<sup>61,62</sup></li> <li>- Brush the teeth twice a day (30 minutes after meal), including before sleep, using fluoride-containing toothpaste or apply fluoride-containing oral gel to the teeth twice a day (I/A)<sup>61,63,64</sup></li> </ul>

**Recommendation 9: Regular, stepwise, and proportional exercise is recommended for SS patients experiencing fatigue**

Fatigue is a very important complaint and one of the most challenging symptoms in pSS. Fatigue was reported in up to 70% of pSS patients, usually being chronic, persistent, and difficult to control.<sup>65-67</sup> Lifestyle management strategies are considered beneficial, including sleep hygiene, daily activity management, relaxation techniques, cognitive behavioral therapy, and stepwise exercise therapy

(including walking and Nordic walking).<sup>61,68,69</sup>

**Recommendation 10: Systemic therapy in SS should be adjusted to the degree of severity and involvement of specific organ based on ESSDAI definition**

The use of systemic therapy (glucocorticoids, antimalarial drugs, immunosuppressive agents, intravenous immunoglobulins, and biologic agents) should be limited to active systemic disease. However, the management of SS with systemic features should

take into account the specific organ involved and its severity based on ESSDAI. Systemic therapy can be considered in most patients that show at least moderate disease activity in one clinical domain, or with moderate global disease activity (total score of more than 5). A favorable response to systemic therapy is typically indicated by a reduction of 3 points in the global ESSDAI score from the previous score.<sup>70,71</sup> It should also be noted that some systemic manifestations are not included in the ESSDAI, such as Ro-associated congenital heart block, Raynaud phenomenon, primary pulmonary hypertension, pleuritis, pericarditis, dysautonomia, interstitial cystitis, and sensorineural hearing loss; therefore, these features will need specific management.<sup>26</sup> Pregnant SS patient should also be managed based on the specific organs affected.<sup>72</sup>

**Recommendation 11: Glucocorticoids should be used with the lowest possible dose in the shortest duration to control active systemic disease in SS. They are not considered as first line drugs**

The frequent use of glucocorticoids in treating pSS is not supported by robust evidence, since there have been no randomized controlled trials specifically evaluating their use in systemic disease. Glucocorticoids should only be used with the lowest dose in the shortest duration to control active systemic disease, and they are not considered as first line drugs. In severe presentations, induction therapy may involve pulse dose methylprednisolone, followed by prednisolone at a dose of 0.5 mg/kg/day or lower. In cases of moderate or less severe presentation, prednisolone can be initiated at a dose of less than 0.5 mg/kg/day, while targeting to gradually stop the usage of glucocorticoids; or if not possible, targeting a maintenance dose of 5 mg/day or less, with the help of glucocorticoid-sparing agents. Up until the time this recommendation was issued, there had been no data that specifically described the specific method to deescalate glucocorticoids dose, timing of glucocorticoid-sparing agent introduction, or the optimal duration of glucocorticoids therapy.<sup>26</sup>

**Recommendation 12: Immunosuppressive agents are mainly used as adjuvants to reduce glucocorticoids usage in SS**

Utilization of glucocorticoids in high dose and long-term duration (especially in patients with severe organ dysfunction) may increase the risk of side effects; in these conditions, immunosuppressive agents can be used as glucocorticoids-sparing agents, while also considering the risk and benefit of the therapy. The use of immunosuppressive agents in pSS were based on the same level of evidence for glucocorticoids, which stated that it can decrease sicca symptoms and improve laboratory parameter, but with no significant effect on systemic disease. The occurrence of side effects in the use of immunosuppressive agents was also quite high, varying from 41-100%. There had been no head-to-head studies which compared the efficacy and safety profiles of different immunosuppressive agents (leflunomide, methotrexate, azathioprine, mycophenolate, cyclophosphamide); therefore, no immunosuppressive agent is more superior than the other. The selection of immunosuppressive agent should be based on the patient's characteristics and comorbidities, necessitating a case-by-case evaluation. No specific recommendation was given by any organization regarding the dosage of immunosuppressive agents or whether they should be given as a monotherapy or combined with glucocorticoids, as the research data was still lacking.<sup>26</sup> The current evidence regarding the use of immunosuppressive agents also showed various results.<sup>73</sup>

**Recommendation 13: Biologic agent therapy can be considered in severe and refractory systemic SS**

Several biologic agents were still under investigation for the use in treating SS. The use of biologic agents can be considered after the failure of immunosuppressive agents. EULAR recommended considering the use of rituximab and belimumab. Rituximab can be considered in systemic pSS patients and in patients with severe refractory systemic disease, such as cryoglobulinemia-related

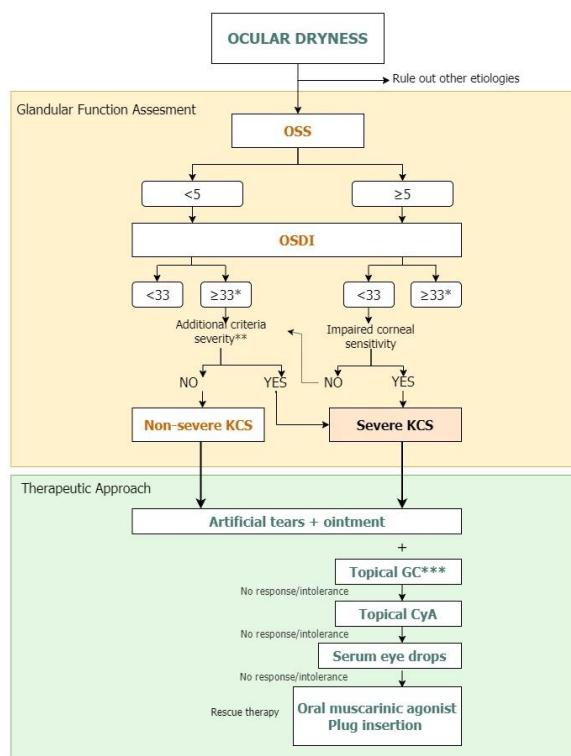
vasculitis.<sup>74</sup> Belimumab can also be considered for systemic pSS, or as a rescue therapy.<sup>75</sup>

**Recommendation 14: Dry eye therapy in SS consists of local and systemic therapy, which are chosen based on the severity of the disease**

The choice of dry eye therapy in SS is usually based on the assessment of OSS (ocular staining score) and OSDI (ocular surface disease index), to determine the severity of keratoconjunctivitis sicca (KCS) in the patient. First line therapies include artificial tears and ointment. Artificial tears containing methylcellulose or hyaluronate are recommended for all SS patients, especially those that do not contain preservatives. The artificial tears can be applied at least twice a day, its frequency can be added as needed. Gel or eye ointment can be an alternative, offering longer effect than artificial tears, but it is advisable to be applied only at

night.<sup>26,61</sup>

In severe KCS, if first line therapy does not offer adequate response, additional therapies such as topical glucocorticoids (GCs) or topical NSAIDs can be considered. However, topical GCs or NSAIDs use should only be limited to 2-4 weeks to prevent side effects. Other additional therapies that are under investigation include topical cyclosporin A or serum eye drops. Plug occlusion and oral muscarinic agonist can be chosen as alternative therapy, if all the other combination therapies do not provide adequate response. The algorithm for choosing therapies for dry eyes in SS can be seen in figure 1. Indonesian Society of Ophthalmologists (PERDAMI) also offered another step-by-step approach in treating dry eyes (including dry eyes in SS), which can be accessed in PERDAMI official website.<sup>26,31,61</sup>



**Figure 1.** Algorithm for glandular function assessment and therapeutic approach in pSS with dry eyes<sup>26</sup>

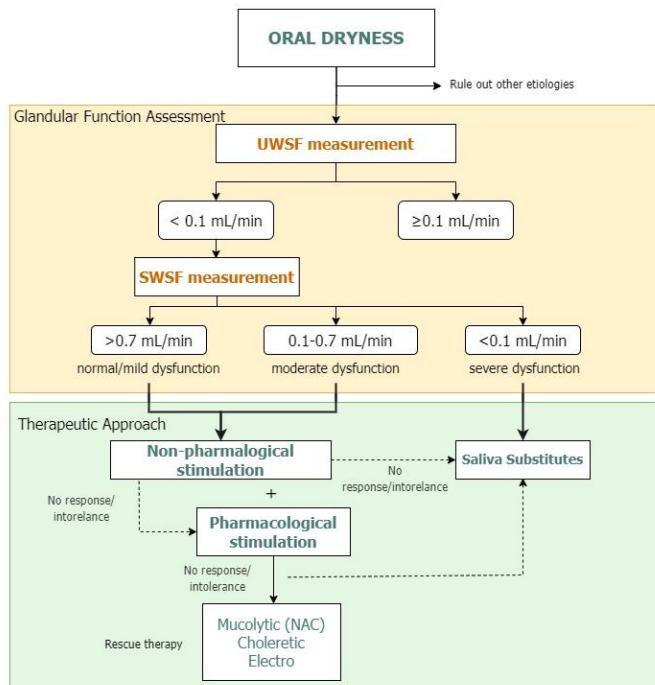
**Recommendation 15: Dry mouth therapy in SS is chosen based on the severity of the disease**

Dry mouth therapeutic approach in SS should be based on salivary gland function assessment.

Xerostomia can be assessed using Summated Xerostomia Index-Indonesia version (SXI-ID), while clinical condition of oral dryness can be assessed using unstimulated whole salivary flow (UWSF) or

clinical oral dryness score (COTS). These assessments should be conducted before initiating therapy and should be periodically re-evaluated during therapy.

Salivary scintigraphy can also be considered.<sup>76-80</sup> The algorithm for glandular function assessment and treatment approach can be seen in Figure 2.



**Figure 2.** Algorithm for glandular function assessment and therapeutic approach in pSS with oral dryness<sup>26</sup>

For patients with mild dysfunction, non-pharmacological stimulation methods are recommended. These may include the use of sugar-free sour candy, lozenges, or xylitol, and/or mechanical stimulation using sugar-free gums.<sup>26</sup> In patients with moderate dysfunction, pharmacological stimulation can be done, using muscarinic agonist such as pilocarpine or cevimeline, though only pilocarpine has been widely approved.<sup>26,81</sup> Pilocarpine can be given 5 mg/day, and its dose can be gradually increased to 20 mg/day, divided into 4 doses, until sicca symptoms are resolved. If these patients do not provide adequate response, choleretic agents (anetholtrithione) or mucolytics (bromhexine, N-acetylcysteine) can be prescribed as secretagogues.<sup>26</sup>

Chlorhexidine is an effective antiseptic that can inhibit plaque formation in the teeth to control gingivitis. Chlorhexidine is also recommended in pSS patients to prevent gum disease, which can be used twice a day, for a maximum duration of 2 weeks, every 3 months. Excessive usage may cause teeth

discoloration.<sup>61,82,83</sup>

Topical fluoride is also very important in preventing dental caries, which can be given in SS patients reporting xerostomia. The application of 5% fluoride varnish was reported to slow or even reverse the process of teeth root caries. Fluoride varnish can be applied in office by dentists. In addition, fluoride-containing toothpaste is also recommended for SS patients with oral dryness. The recommended fluoride concentration in the toothpaste is 500-1000 ppm.<sup>61,82,84,85</sup>

Sucking sugar-free hard candies or gums may help stimulate saliva production. These candies or gums often contain baking soda to neutralize acids, xylitol to prevent dental caries, and green tea extract for its antioxidant effect. Xylitol is an unfermentable carbohydrate which can increase oral cavity pH, coat teeth surface, and reduce the risk of dental caries for up to 10%. Therefore, xylitol is recommended to prevent tooth decay.<sup>61,63,84</sup>

Patients with decreased saliva production are at an

increased risk for oral candidiasis, since saliva often contains antimicrobial proteins that prevent *C. albicans* attachment to oral epithelium. Risk for oral candidiasis is also increased in patients using dentures, especially those with poor oral hygiene. The environment between oral mucosa and denture-bearing area is often low in oxygen and saliva, with low pH, which increases the activity of secreted aspartyl proteinases (SAP). SAP is an enzyme secreted by *C. albicans* to destroy host cell membrane and help *C. albicans* to avoid host immune system. Loose denture may also cause mucosal injury which then cause damage in the mucosal barrier, therefore allowing *Candida* colony infiltration, causing infection.<sup>86</sup>

Oral candidiasis may appear as oral thrush, acute erythematous candidiasis, chronic atrophic erythematous candidiasis (denture stomatitis), cheilitis angularis, candida leukoplakia, or atrophic glossitis. Patients with denture stomatitis are recommended to maintain good oral and denture hygiene, by removing dentures at night, using disinfecting mouthwash (such as chlorhexidine, hexetidine, and essential oil), using denture cleaner, and relining the denture periodically.<sup>86</sup>

Pharmacological therapy for oral candidiasis can involve topical or systemic therapies. Topical therapy includes medication application to the infected area. The recommended topicals are 100,000 IU nystatin, 4x6 ml, or nystatin oral gel, 4 times a day for 1-2 weeks. Other topical therapies include oral miconazole gel (4 times a day), miconazole mucoadhesive tablets (one 50 mg tablet a day), clotrimazole 1% gel (3 times a day), and ketoconazole 2% gel (3 times a day).<sup>86-91</sup>

The first choice of systemic therapy for oral candidiasis is 50-100 mg of fluconazole once a day, for 7-14 days for moderate to severe cases. Other choices are 100-200 mg of itraconazole (once a day for 4 weeks), 400 mg of posaconazole (twice a day for 3 days, continued with once daily for 4 weeks), 200 mg of voriconazole (twice a day for 14 days), and 200 mg of ketoconazole once daily. In recurrent oral candidiasis, 100 mg of fluconazole can be given three times a week.<sup>87,91,92</sup>

**Recommendation 16: Salivary gland edema in SS can be treated with short-term oral prednisolone or intramuscular methylprednisolone in acute inflammation, and gland massage in chronic inflammation**

Initial ultrasound examination can be considered to assess active inflammation, infection, and salivary gland stones. Ultrasound examination in the salivary gland can also provide information regarding edema in the gland and can also differentiate between benign and malignant lesion. Short term oral prednisolone or intramuscular methylprednisolone injection (120 mg) can be given to help relieve salivary gland edema (without the presence of stones or infection). Salivary gland massage has been shown to help relieve discomfort in chronic salivary gland inflammation.<sup>61</sup>

**Recommendation 17: Non-hormonal vaginal moisturizer, with or without topical estrogen, is recommended for SS patients with vaginal dryness**

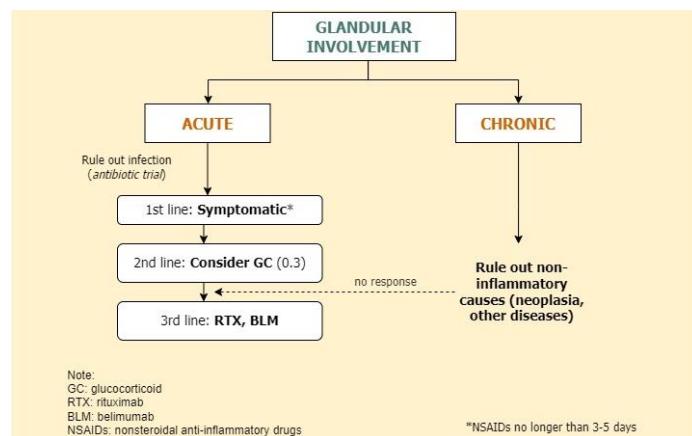
Women with SS often complain of vaginal dryness. Pilocarpine has demonstrated ability to stimulate glandular secretion. Non-hormonal vaginal moisturizer is also recommended in these patients, which can help relieve problems such as itchiness, vaginal irritation, and dyspareunia. Products containing topical estrogen were also shown to be beneficial in treating vaginal dryness in postmenopausal women with SS. These products include cream and pessaries. There was a risk of systemic absorption of these topical hormones, but current evidence has shown no risk of endometrial thickening.<sup>61</sup>

**Recommendation 18: Organ specific therapy approach for specific organ manifestations (glandular, articular, skin, pulmonary, renal, peripheral neuropathy, central nervous system, hematological) in SS includes the use of glucocorticoids, immunosuppressive agents, biologic agents, and combination therapy**

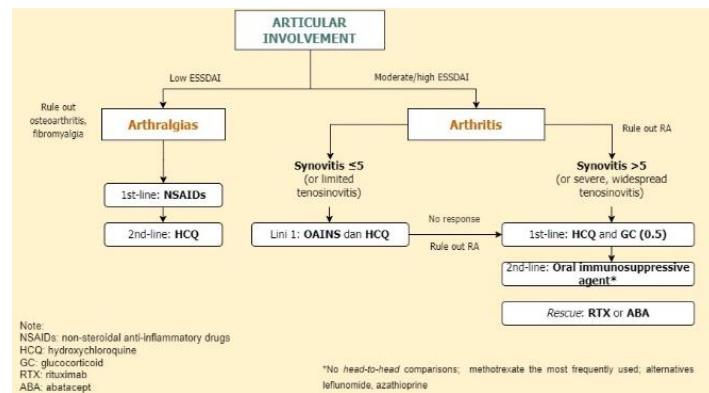
In general, there are three groups of systemic therapies that can exert immunosuppressive effects,

which are glucocorticoids, immunosuppressive agents, and biologic agents. Most SS patients with active systemic disease are given glucocorticoids as the first-line therapy. Meanwhile, immunosuppressive and biologic agents are chosen as second- or third-line therapy, especially in patients who are intolerant or refractory to glucocorticoids, patients with severe symptoms, or in patients anticipated to receive long-

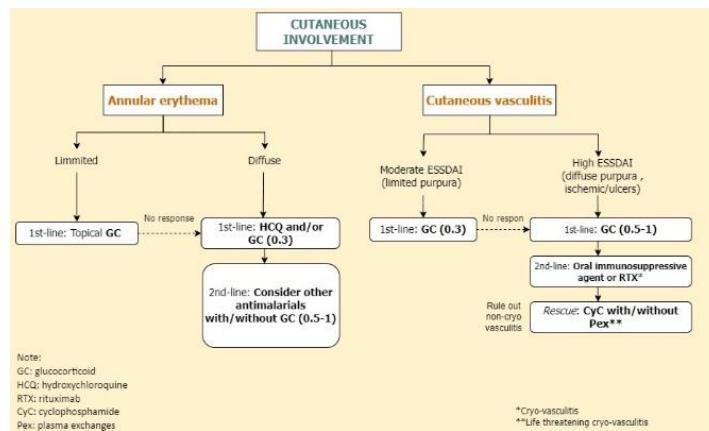
term glucocorticoids. A set of algorithms were compiled by EULAR for choosing therapy based on specific organ manifestations, including glandular, articular, cutaneous, pulmonary, renal, peripheral neuropathy, central nervous system, and hematological manifestations.<sup>26</sup> These adapted algorithms can be seen in Figures 3 to 10.



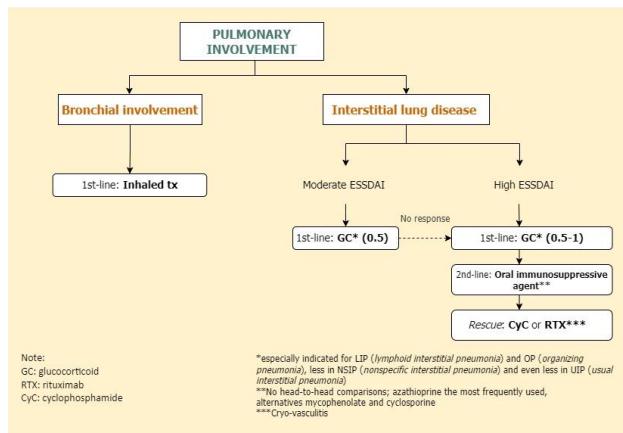
**Figure 3.** Algorithm for choosing systemic therapy in SS with glandular involvement



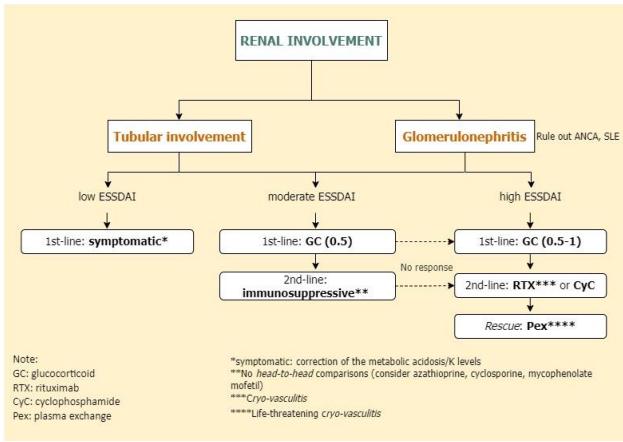
**Figure 4.** Algorithm for choosing systemic therapy in SS with articular involvement



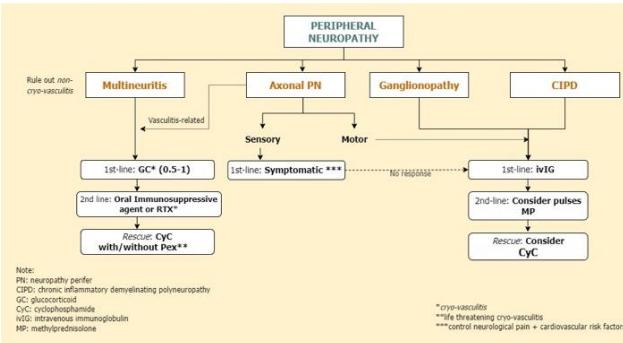
**Figure 5.** Algorithm for choosing systemic therapy in SS with cutaneous involvement



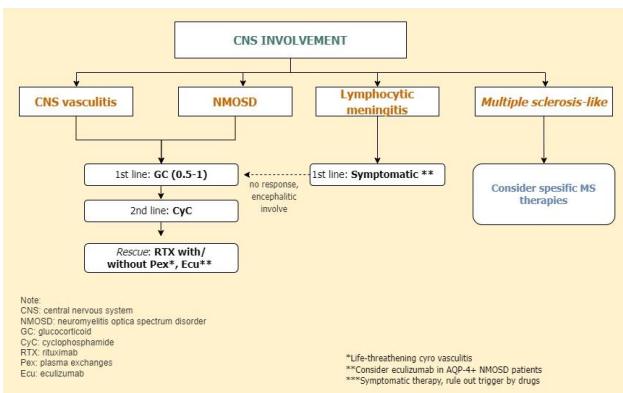
**Figure 6.** Algorithm for choosing systemic therapy in SS with pulmonary involvement



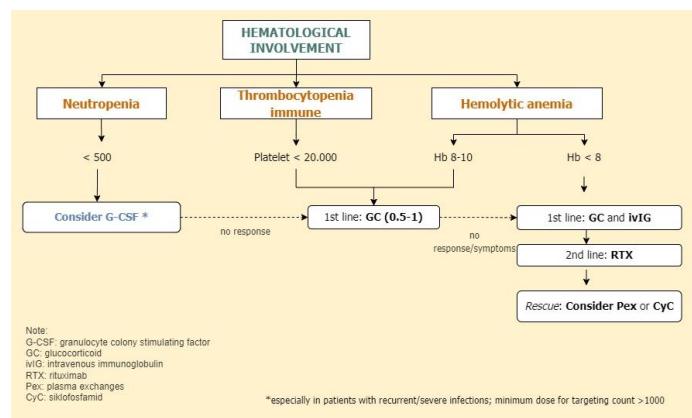
**Figure 7.** Algorithm for choosing systemic therapy in SS with renal involvement



**Figure 8.** Algorithm for choosing systemic therapy in SS with peripheral neuropathy



**Figure 9.** Algorithm for choosing systemic therapy in SS with central nervous system involvement



**Figure 10.** Algorithm for choosing systemic therapy in SS with hematological involvement

**Recommendation 19: SS prognostic factors are assessed from disease activity, extra-glandular involvement, low complement levels, the presence of cryoglobulinemia, and other comorbidities**

Known prognostic factors for SS patients are disease activity, extra-glandular manifestation, low complement levels, the presence of cryoglobulinemia, and the presence of other comorbidities. Reports regarding mortality in SS were still inconclusive, but it was generally considered that there was no increased mortality in SS patients.<sup>93-95</sup> Extra-glandular manifestation was reported to significantly decrease the patients' quality of life.<sup>93,96</sup>

Several factors that may predict worse prognosis in SS patients include older age onset at diagnosis, polyarthritis, vasculitis, Raynaud phenomenon, lymphoma (the grade and size of the tumor itself), solid tumor, low complement level (C3 and C4), cryoglobulinemia, interstitial lung disease, renal involvement, parotid gland enlargement, and abnormal parotid scintigraphy.<sup>93,96-98</sup> Severe exocrine gland disease has been associated with an increased risk of developing lymphoma. Patients with cutaneous vasculitis were also reported to have increased mortality risk due to lymphoma complication. Low level of complement, especially C4, was associated with increased risk of premature death.<sup>94</sup> In patients with ILD, worse prognosis has been observed in patients with purpura, low level of C4, mixed monoclonal cryoglobulinemia, pulmonary hypertension, and lymphoma. Wide reticular changes

in HRCT imaging and multiple fibroblast foci in lung biopsy were also related to worse prognosis.<sup>99,100</sup>

Several parameters were associated with increased risk of developing non-Hodgkin lymphoma (NHL), which are clinical, hematological, serological, and histopathological parameters on the onset of SS diagnosis. Patients with SS have 7-19 times higher risk for developing NHL. The risk factors include salivary gland enlargement, lymphadenopathy, Raynaud phenomenon, positive anti-SSA or anti SS-B, positive rheumatoid factor, monoclonal gammopathy, and low C4 level.<sup>101</sup>

## 5. Conclusion

These recommendations are formulated to provide guidance on the diagnosis and management of Sjogren's syndrome in Indonesia. The diagnostic, therapeutic, and monitoring algorithms outlined in this recommendation have been tailored to align with Indonesia's clinical setting, facility, and drug availability. We hope that these recommendations can serve as guidelines for every physicians in Indonesia to facilitate management of Sjogren's syndrome patients.

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