Consensus Guidelines for Evaluation and Management of Pulmonary Disease in Sjögren's

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BACKGROUND: Pulmonary disease is a potentially serious yet underdiagnosed complication of Sjögren's syndrome, the second most common autoimmune rheumatic disease. Approximately 16% of patients with Sjögren's demonstrate pulmonary involvement with higher mortality and lower quality of life.

RESEARCH QUESTION: Clinical practice guidelines for pulmonary manifestations of Sjögren's were developed by the Sjögren's Foundation after identifying a critical need for early diagnosis and improved quality and consistency of care.

STUDY DESIGN AND METHODS: A rigorous and transparent methodology was followed according to American College of Rheumatology guidelines. The Pulmonary Topic Review Group (TRG) developed clinical questions in the PICO (Patient, Intervention, Comparison, Outcome) format and selected literature search parameters. Each article was reviewed by a minimum of two TRG members for eligibility and assessment of quality of evidence and strength of recommendation. Guidelines were then drafted based on available evidence, expert opinion, and clinical importance. Draft recommendations with a clinical rationale and data extraction tables were submitted to a Consensus Expert Panel for consideration and approval, with at least 75% agreement required for individual recommendations to be included in the final version.

RESULTS: The literature search revealed 1,192 articles, of which 150 qualified for consideration in guideline development. Of the original 85 PICO questions posed by the TRG, 52 recommendations were generated. These were then reviewed by the Consensus Expert Panel and 52 recommendations were finalized, with a mean agreement of 97.71% (range, 79%-100%). The recommendations span topics of evaluating Sjögren's patients for pulmonary manifestations and assessing, managing, and treating upper and lower airway disease, interstitial lung disease, and lymphoproliferative disease.

INTERPRETATION: Clinical practice guidelines for pulmonary manifestations in Sjögren's will improve early identification, evaluation, and uniformity of care by primary care physicians, rheumatologists, and pulmonologists. Additionally, opportunities for future research are identified.

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KEY WORDS: guideline; lung; pulmonary; Sjögren; Sjögren's

ABBREVIATIONS: ACR = American College of Rheumatology; CTD = connective tissue disease; CEP = Consensus Expert Panel; DLCO = diffusing capacity of the lung for carbon monoxide; EULAR = European League Against Rheumatism; HRCT = high-resolution CT; ILD = interstitial lung disease; MALT = mucosa-associated lymphoid tissue; NYHA = New York Heart Association; PICO = Patient, Intervention, Comparison, Outcome; PFT = pulmonary function test; TRG = Topic Review Group; UIP = usual interstitial pneumonia

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Pulmonary disease is a potentially serious yet underdiagnosed complication of Sjögren's syndrome, a chronic autoimmune disease with substantial disease morbidity and burden as well as reduced quality of life.[1,2] Sjögren's not occurring with another autoimmune disease has a prevalence second only to rheumatoid arthritis among the inflammatory rheumatic illnesses,[3] and although the disease can be observed in children and men,[4] it is most prevalent in women.[5]

Clinical practice guidelines for the diagnosis, management, and treatment of pulmonary manifestations of Sjögren's were developed by the Sjögren's Foundation after identifying a critical need for early diagnosis and improved quality and consistency of care. Approximately 10% to 20% of Sjögren's patients demonstrate pulmonary involvement with an associated higher mortality and lower quality of life.[6-11] In addition, up to 65% of asymptomatic Sjögren's patients will have abnormal pulmonary imaging,[7] emphasizing the need for provider awareness of pulmonary manifestations and education on evaluation, monitoring, and treatment. Pulmonologists are encouraged to consider the possibility of Sjögren's in patients with pulmonary disease who have not previously been diagnosed as having Sjögren's. As such, pulmonologists can play an important role in Sjögren's diagnosis and ensure that nonpulmonary complications of Sjögren's are addressed by the appropriate specialists.

Materials and Methods

A rigorous and transparent methodology was followed according to the American College of Rheumatology (ACR) guidelines.[12] The methodology employed for these guidelines was first developed and used by the Foundation for recommendations for rheumatologic management in Sjogren's[13] and included direction from the ACR as well as other guidelines methodology consultants.[14] The Pulmonary Topic Review Group (TRG) included equal parts rheumatologists and pulmonologists (n = 4 each) and one hematologist-oncologist as well as participation and oversight by a rheumatologist chair for all Foundation guidelines and a rheumatology/systemic symptoms guidelines chair. The TRG defined systematic review parameters and end points (e-Appendix 1), including MEDLINE/PubMed peer-reviewed articles in English between January 1, 1990, and February 1, 2020, and studies with Sjögren's patients classified or diagnosed by any published set of criteria. Although currently either the 2002 American-European Consensus Group[15] or the 2016 ACR/European League Against Rheumatism (EULAR)[16] classification criteria for primary Sjögren's are utilized most often, a number of criteria have been used historically.

An outline with clinical questions was developed based on the PICO (Patient, Intervention, Comparison, Outcome) format (e-Appendix 2). For the systematic review, literature search terms were compiled by the TRG, and the searches were executed by a librarian (e-Appendix 1). Each article was reviewed by a minimum of two TRG members for eligibility and assessment of quality of evidence. Full data were extracted into four tables: Study Characteristics, Sample and Disease, Evidence, and Quality (https://www.sjogrens.org/researchers-providers/clinical-practice-guidelines). The Quality table rated the overall quality of each study according to criteria related to study design and the risk of bias used in recommendation development.

Guidelines were drafted based on available evidence using a strength of the evidence rating (e-Appendix 3), the expertise of the TRG and Consensus Expert Panel (CEP) members who reviewed the recommendations, and clinical importance. Each recommendation also was rated for the strength of the recommendation, which was gauged by the TRG based on a combination of available evidence as well as the confidence level that the recommendation offers the best current guidance for practice.

Draft recommendations and strength of the recommendation were submitted to the CEP for consideration and approval, with at least 75% agreement required for inclusion in the manuscript. A clinical

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An abstract on the formation of the Topic Review Group and areas to be covered was presented in a poster format at the 2018 International Symposium on Sjögren's Syndrome, April 18-21, 2018, Washington, DC. A poster was accepted for the May 2020 ATS annual meeting, which was rescheduled as a virtual meeting. An updated poster was uploaded on July 30, 2020, for the later meeting.

DISCLAIMER: The Sjögren's Foundation developed these Clinical Practice Guidelines with an expert group of rheumatologists and pulmonologists and an oncologist to help guide ALL health-care providers in managing and treating pulmonary manifestations of Sjögren's patients. They are not intended to prescribe care for individual patients and may not apply to certain clinical scenarios or take into account the nuances of clinical care. These guidelines are intended for Sjögren's and lung disease and may not apply to those with other systemic autoimmune disorders. Clinicians are asked to weigh various factors, including unique patient-specific nuances, patient preferences, and cost, in their decision-making when considering these Recommendations.

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rationale for each recommendation and data extraction tables for articles used in developing the recommendations also were provided. The CEP, composed of 68 members (including 40 rheumatologists, 21 pulmonologists, and seven additional members, all of whom were Sjögren's patients or family of patients [e-Appendix 4]), voted on each recommendation using a six-point Likert scale, the strength of the recommendation (rating), and provided commentary for TRG review. If the consensus threshold was not met, the recommendation would be adjusted by the TRG until the consensus threshold was met. The commentary provided by the CEP was considered in the final wording of the recommendations and clinical rationales. Recommendations were again evaluated by the CEP following minor wording changes to better align with standard guideline language.

The formal consensus process was deemed especially critical in view of the lack of high-quality evidence. The guidelines committee utilized principles of the American Society of Clinical Oncology, Grading of Recommendations Assessment, Development and Evaluation, Agency for Health Research and Quality, and the US Preventive Services Task Force to formulate the methodology.

Results

The TRG originally developed 85 topics/questions in the PICO format that spanned epidemiology, evaluation, diagnostics, and therapeutics of Sjögren's-related pulmonary manifestations, including upper and lower airway disorders, interstitial lung diseases, pulmonary vascular disease, and lymphoproliferative disorders. The number of questions was reduced after TRG members ranked all clinical questions as Primary, Secondary, or Minor in terms of the question's importance for recommendation development, and final selection was determined by TRG leadership when consensus was lacking. Following the literature search, some PICO questions were determined to be irrelevant and/or not suited to recommendations for a pulmonary condition or to be within the scope of this paper.

Medical literature searches utilizing the predefined search terms and search criteria (e-Appendix 1) identified 1,192 articles, of which 178 abstracts were selected and 150 of those deemed qualified for data extraction and use in guideline development. Abstracts identified by the literature search but eliminated by the TRG were excluded for the following reasons: not relevant to guidelines (such as unrelated to Sjogren's and/or pulmonary), article type (commentary, editorial, letter to the editor), case studies that provided no unique information, or were not in English (e-Appendix 1, Quorum Diagram).

The TRG then generated 52 recommendations along with a rating on the strength of each recommendation that was submitted to the CEP. A clinical rationale for each recommendation (e-Appendix 5), and all references with data extracted were provided in support of the recommendations. The consensus threshold of 75% was achieved for all 52 recommendations and ratings in one round, with agreement ranging from 79% to 100% for 102 questions (52 recommendations and 52 ratings) and an average agreement of close to 98%. The CEP results are provided in e-Appendix 4. Additionally, commentaries provided by the CEP were reviewed by the TRG and led to rewording 12 recommendations and 13 clinical rationales without altering their substance. Because these recommendations were intended to be wide-reaching and used across multiple specialties, the authors preferred to make firm recommendations and avoided vaguer terms such as "may be considered" when reasonable.

Evaluation for Lung Involvement

Consensus recommendations on evaluating Sjögren's patients for potential pulmonary signs and symptoms and the use of imaging, full (complete) pulmonary function tests (PFTs), which includes spirometry, diffusing capacity of the lung for carbon monoxide (D_{LCO}), and lung volumes ideally measured by body plethysmography, and bronchoscopy are listed in Table 1 and Figure 1. In addition, we have provided practical clinical guides to assist in the history taking and symptom detection for evaluation purposes in e-Appendix 6. An additional consideration that was borne out of the literature review was that Sjögren's is often diagnosed after a pulmonary disorder is initially recognized. These include patients with airway disorders (eg, refractory cough, small airway disease), indeterminate interstitial lung diseases (ILD), and pulmonary lymphoproliferative disorders (eg, mucosa-associated lymphoid tissue [MALT]-type lymphoma). Table 2 provides a list of Sjögren's symptoms for the clinician to consider when the etiology of a patient's pulmonary condition remains undiagnosed.

Since lung involvement is common in Sjögren's, a baseline chest radiograph is recommended. If concern is high for lung involvement, however, a high-resolution CT (HRCT) scan may be preferred due to its higher sensitivity and specificity.[17,18] Full PFTs as described above may additionally identify patients with subclinical Sjögren's lung disease.[19] Although few outcomes data exist, a baseline chest radiograph and full PFTs were recommended by the TRG and the CEP when weighing the risks and benefits, as these tests are likely to aid in identifying subclinical disease, in future comparisons

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TABLE 1] Recommendations for Evaluating Patients With Sjögren's

Recommendation	Strength of Evidence	Strength of Recommendation
Recommendations: Evaluating asymptomatic Sjögren's patients for pulmonary complications		
1. Serologic biomarkers must not be employed to evaluate for pulmonary involvement in patients with established Sjögren's disease.	INTERMEDIATE	STRONG
2. Due to the prevalence of respiratory involvement in Sjögren's, clinicians must obtain a detailed medical history inquiring about respiratory symptoms in all Sjögren's patients at the initial and every subsequent visit.	HIGH	STRONG
3. In Sjögren's patients without respiratory symptoms, a baseline two-view chest radiograph may be performed. The baseline chest radiograph can (1) help identify pulmonary involvement despite the absence of symptoms, (2) identify alternate etiologies of sicca symptoms such as sarcoidosis, vasculitis, and lymphoma, and (3) serve as a baseline for future comparisons.	INTERMEDIATE	WEAK
4. In Sjögren's patients who have no respiratory symptoms, baseline complete PFTs* may be considered to evaluate for the presence of underlying pulmonary manifestations. PFTs should include pre- and post-bronchodilator spirometry, lung volumes, and diffusing capacity of the lung for carbon monoxide. Abnormalities identified may require further corroboration with advanced testing.	INTERMEDIATE	WEAK
5. In asymptomatic Sjögren's patients, routine echocardiogram is not recommended.	INTERMEDIATE	STRONG
Recommendations: Evaluating Sjögren's patients with pulmonary symptoms		
1A. In Sjögren's patients with chronic cough and/or dyspnea, complete PFTs and HRCT should be done to evaluate for pulmonary involvement.	INTERMEDIATE	MODERATE
1B. In a Sjögren's patient with respiratory symptoms, the interval for repeat HRCT and PFTs must be determined on a case-by-case basis and individualized according to the nature and severity of the underlying pulmonary abnormality and the degree of symptoms and functional impairment.	INSUFFICIENT	STRONG
2. In a Sjögren's patient with dyspnea, an echocardiogram is recommended in the following circumstances: a) In patients with suspected pulmonary hypertension b) In patients with unexplained dyspnea after pulmonary etiologies (asthma, small airway disease, bronchiectasis, ILD) have been excluded c) In patients with suspected cardiac involvement	HIGH	STRONG
3. In a Sjögren's patient with respiratory symptoms, a CTPA to look for pulmonary embolism must not be performed routinely in all patients but rather dictated by clinical suspicion for pulmonary embolism in individual circumstances. If clinically concerned about a pulmonary embolism, CTPA is the confirmatory test of choice. Ventilation-perfusion scan should only be considered in the following circumstances: a) To rule out chronic thromboembolic pulmonary hypertension in patients with pulmonary hypertension b) When clinical concern for pulmonary embolism exists, and a physician is unable to do a CTPA because of patient allergy to contrast or renal insufficiency	LOW	STRONG
Recommendations: Evaluating for Sjögren's in patients with lung disease		
1. In patients who have an uncharacterized ILD, diffuse cystic lung disease, or pulmonary lymphoma, clinical and serologic evaluation for Sjögren's is recommended.	HIGH	STRONG
Recommendations: Use of bronchoscopy		
1. In a Sjögren's patient with respiratory symptoms, bronchoscopy with BAL must not be performed routinely but determined on a case-by-case basis and limited to special circumstances, such as the need to: a) Rule out infectious etiologies, especially in patients on immune suppression b) Rule out endobronchial abnormalities such as amyloidosis in patients with chronic cough not otherwise responsive to treatment c) Distinguish between other etiologies of sicca symptoms such as sarcoidosis	LOW	STRONG
2. In a Sjögren's patient with respiratory symptoms, use of bronchoscopy with endobronchial biopsies and transbronchial lung biopsy are not recommended for routine use.	INSUFFICIENT	STRONG

CTPA = CT pulmonary angiogram; ILD = interstitial lung diseases; PFTs = pulmonary function tests.

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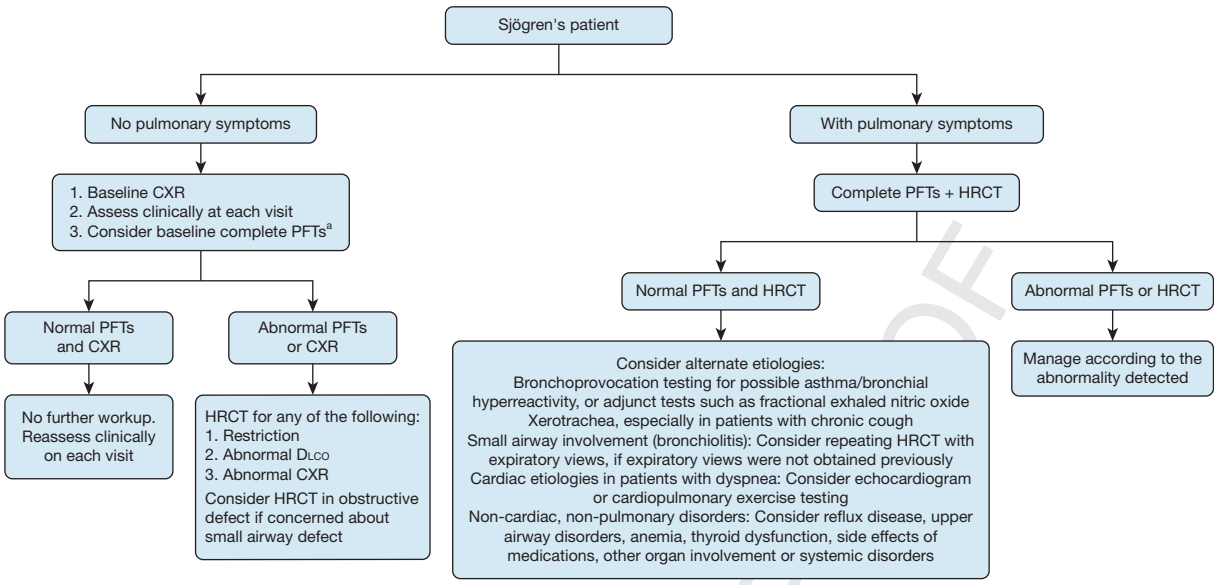

Figure 1 – *Respiratory evaluation for Sjögren's patients. [a]The benefit of obtaining baseline PFTs in asymptomatic Sjögren's patients regarding long-term outcomes is not clear. This paucity of evidence and the potential costs of the test should be taken into account and discussed with individual patients prior to proceeding with PFTs. Complete PFTs includes spirometry, DLCO, and lung volumes, ideally measured by body plethysmography. CXR = chest radiograph; DLCO = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution CT; PFTs = pulmonary function tests.*

when symptoms develop, and in guiding the timing of any specific interventions.

In general, all symptomatic patients should have serial clinical and PFT monitoring. However, monitoring strategy depends on the clinician's consideration of the specific condition, its severity, the patient's symptoms and functional status, and the pace of clinical deterioration. While no specific guidance regarding intervals for repeat testing can be given, the majority of TRG members repeat PFTs at least every 6 to 12 months to better understand longitudinal disease trajectory. Typically, spirometry is performed as the main monitoring test at each interval, with complete PFTs,

TABLE 2] Evaluating for Potential Sjögren's in Patients with Pulmonary Symptoms

Symptom	Questions to Ask Patient
Oral symptoms	• Does your mouth feel dry? • Do you need liquids to swallow dry foods? • Do you frequently sip/drink water? • Do you have a burning sensation in the mouth? • Do you have painful sores or red patches at the corners of the mouth (angular cheilitis)? • Do you get frequent dental cavities, particularly gumline cavities? • Do your teeth tend to chip, crack, and/or erode on the surfaces? • Do you suffer from gum inflammation or receding gums (gingivitis?)
Ocular symptoms	• Do your eyes frequently feel dry, irritated, itchy, or painful? • Do you have a sensation that there might be a foreign body in your eye? • Are your eyes light sensitive? • Do you frequently use eye drops for irritation or dryness? • Is your vision frequently blurry, or do you have unexplained vision changes?
Other symptoms	• Have you noticed gland swelling in your face or along the jaw line (swollen parotid and/or submandibular glands)? • Do you suffer dryness of the vagina (is intercourse painful?) or skin (is your skin itchy or flaking?)? • Do your feet, legs, or hands ever feel numb, have a change in sensation, or have burning pain (peripheral neuropathy)? • Do you suffer from extreme fatigue? • Do your joints or muscles ache when you are not sick (arthralgias, myalgias)? • Do you ever notice your fingers turning pale or blue in the cold (Raynaud's disease)?

Symptoms should prompt the physician to engage in further serologic evaluation and/or rheumatology consultation.

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TABLE 3] Recommendations for Assessment and Management of Upper and Lower Airway Disease in Sjögren's Patients

Recommendations: Assessment and Management of Upper and Lower Airway Disease in Sjögren's Patients	Strength of Evidence	Strength of Recommendation
1. In Sjögren's patients with symptomatic vocal cord cystic lesions ("bamboo nodules"), less aggressive interventions, including voice therapy, inhaled corticosteroids, or intra-lesional corticosteroid injection, should be tried first. Surgical resection should be considered if initial measures fail, with consultation by a laryngologist with experience in Sjögren's.	LOW	MODERATE
2. Sjögren's patients with dry bothersome cough and documented absence of lower airway or parenchymal lung disease must be assessed for treatable or preventable etiologies other than xerotrachea, including gastroesophageal reflux, postnasal drip, and asthma.	INTERMEDIATE	STRONG
3. In a Sjögren's patient with dry, nonproductive cough, humidification, secretagogues, and guaifenesin may be empirically initiated after exclusion of other causes.	INSUFFICIENT	WEAK
4. The use of humidification for improving positive airway pressure tolerance and compliance may be recommended in Sjögren's patients.	INSUFFICIENT	WEAK
5. Smoking cessation is recommended in all Sjögren's patients.	INTERMEDIATE	STRONG
6A. In Sjögren's patients with symptomatic small airway disease, bronchoscopic biopsy is not recommended as part of routine assessment or evaluation.	INSUFFICIENT	STRONG
6B. In Sjögren's patients with symptomatic small airway disease, complete pulmonary function testing must be performed to assess severity of small airway disease, and high-resolution CT imaging with additional expiratory views can be helpful in suggesting its presence.	INSUFFICIENT	STRONG
7. In Sjögren's patients with small airway disease, time-limited empiric therapy in newly diagnosed and previously untreated disease may include: • A short course of systemic steroids for 2-4 weeks with a repeat spirometry to determine reversibility, especially if uncontrolled asthma is suspected • Nebulized or inhaled short or long-acting bronchodilators and/or inhaled corticosteroids if there is physiological obstruction • Short course (ie, 2-3 months) of empiric macrolide antibiotics (most commonly azithromycin 250 mg 3 days a week) for persistent, nonreversible, symptomatic bronchiolitis	LOW	WEAK
8. It is recommended that Sjögren's patients with clinically relevant bronchiectasis be treated similarly to those with primary or secondary bronchiectasis of other etiologies and may include any of the following: • Mucolytic agents/expectorants • Nebulized saline or hypertonic saline • Oscillatory positive expiratory pressure • Postural drainage • Mechanical high-frequency chest wall oscillation therapies • Chronic macrolides in those without non-tuberculous mycobacterium colonization or infection	LOW	STRONG

which include lung volumes and DLCO performed at longer intervals.

Upper and Lower Airway Disorders

Upper and lower airway disease reported in association with or as a result of Sjögren's includes xerotrachea, dysphagia, laryngopharyngeal reflux, vocal cord cystic lesions ("bamboo nodules"), OSA, bronchiectasis, bronchiolitis, obstructive lung disease, and reactive airway disease. Approximately 38% of Sjögren's patients have chronic cough.[20] Interestingly, among patients without an initial Sjögren's diagnosis, an unexplained cough associated with dry eyes led to confirmation of Sjögren's in 36%.[21] An evaluation is warranted in a Sjögren's patient with chronic cough (> 8 weeks), starting with an assessment for common causes (eg, asthma, gastroesophageal reflux disease, upper airway cough syndrome, non-asthmatic eosinophilic bronchitis),[22] followed by evaluation of pulmonary complications of Sjögren's, including xerotrachea, ILD, bronchiolitis, bronchiectasis, and pulmonary lymphoma.

Small airway disease in the setting of Sjögren's may represent histopathologic follicular or constrictive

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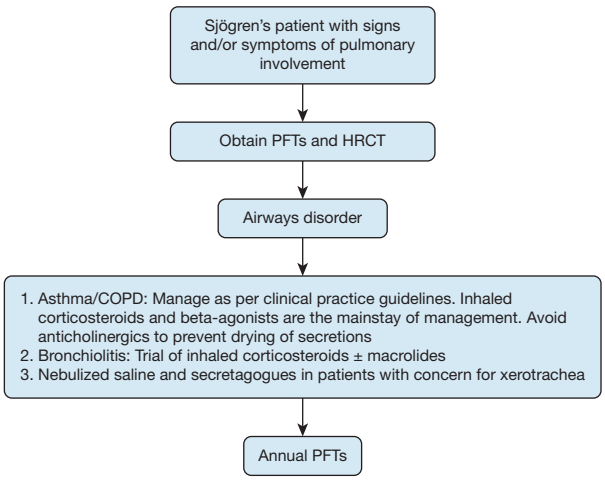

Figure 2 – *Evaluation and management of patients with Sjögren's who exhibit symptoms and/or physical examination signs of pulmonary involvement.*[26,27] *Details regarding Figure 1 for details regarding PFTs and HRCT examinations are given in Figure 1. HRCT = high-resolution CT; pulmonary function tests.*

bronchiolitis.[23] Although there is often overlap on imaging and physiology, these distinctive histologic findings have variable types of inflammation (neutrophilic, lymphocytic, eosinophilic, fibroblast) and bronchiolocentric fibrosis. Bronchiectasis is characterized radiographically by the atypical dilation of the airways larger than the accompanying bronchial artery, or visible to 1 cm of the costal pleural margin. Inhaled corticosteroids, while possibly increasing the risk for candidiasis, have been recommended for inflammatory airway disease by the 2020 EULAR recommendations for managing Sjögren's.[24] Bronchodilators may be tried empirically. And, while no broadly accepted criteria exist for xerotrachea, following exclusion of other causes of cough, empirical humidification in all Sjögren's patients with chronic cough is recommended along with consideration of an empiric trial of a secretagogue and/or guaifenesin. Most of these and other recommendations as listed in Table 3 largely draw upon experience from related airway disorders outside of the specific context of Sjögren's. Figure 2 is a suggested clinical pathway based on these recommendations.[25,26]

Interstitial Lung Disease

Most Sjögren's patients who have ILD exhibit pulmonary symptoms such as shortness of breath, cough, sputum production, or chest pain.[6] Symptom severity varies from asymptomatic to minimal dyspnea on exertion to severe. The onset of ILD increases over time, with one study showing a prevalence of 10% within the first year of diagnosis and 20% after 5 years.[8] Among Sjögren's patients with ILD, specific subtypes that have been reported include: nonspecific interstitial pneumonia 45%, respiratory bronchiolitis 25%, usual interstitial pneumonia (UIP) 16%, lymphoid interstitial pneumonia 15%, organizing pneumonia 7%, amyloid 6%, and lymphoma 4%.[6]

Cystic lung disease is found more commonly in Sjögren's compared with the other connective tissue diseases (CTDs). Martinez-Balzano et al[27] reported that cystic lung disease was associated with older age, a diagnosis of secondary Sjögren's, and elevated anti-SSA (or Ro) antibody, whereas Lechtman et al[28] reported a higher frequency of anti-SSB (or La) antibody. Pulmonary function testing was nonspecific, and no significant radiographic progression was noted (n = 12) after a median follow-up of 4 years. Two patients had secondary infections complicating the cysts, but pneumothoraces appeared to be an uncommon presentation of cystic lung disease. The prognosis of cystic lung disease in Sjögren's depends on the specific histopathologic findings. Cystic lung disease in Sjögren's is most commonly secondary to lymphoid interstitial pneumonia/follicular bronchiolitis but might also suggest the presence of amyloid or MALT lymphoma, especially if associated with concomitant nodules.[29]

A large proportion of the ILDs in Sjögren's tend to follow an indolent course. However, ILD with a UIP pattern in Sjögren's can be progressive and portend a worse prognosis.[30,31] Acute exacerbations of nonspecific interstitial pneumonia and UIP have been reported and can precipitate respiratory failure and death. Most cases do not require biopsy confirmation, as the diagnosis usually can be made based on HRCT and PFTs, and treatment is not always necessary.[30] Ito et al[32] reported that mortality is associated with decreased baseline Pa_{O_2} and presence of microscopic honeycombing. A large retrospective cohort from Taiwan[33] of 4,954 Sjögren's patients reported that the incidence of respiratory failure was higher than in non-Sjögren's patients, regardless of sex, age, and comorbidities. Respiratory failure in primary Sjögren's was most commonly attributed to ILD (25%), followed by small airway disease (22%), desiccation of upper respiratory tract (17%), and large airway obstruction (8%).

When obtaining baseline PFTs, it should be noted that discordance between PFT abnormalities, degree of symptoms, and HRCT findings can occur.[7,34,35] Additionally, patients with ILD have variable natural history of disease progression. While evidence is unavailable on the frequency or duration of PFTs in

TABLE 4] Recommendations for ILD in Sjögren's Patients

Recommendation	Strength of Evidence	Strength of Recommendation
Recommendations: ILD—diagnosis, evaluation, and management		
1. In a Sjögren's patient with suspected ILD, an HRCT with expiratory views is recommended.	HIGH	STRONG
2. In a Sjögren's patient with suspected ILD, oximetry testing is recommended as part of a patient's initial evaluation.	HIGH	STRONG
3. Baseline PFTs must be performed in all Sjögren's patients with suspected or established ILD and followed initially at 3- to 6-month intervals for at least 1 year. Subsequent testing requires consideration of the type of ILD, the clinical course, and the pace of change noted on the serial PFTs. The baseline PFTs should include lung volumes by body plethysmography, spirometry, diffusing capacity, and oxygen saturations at rest and exercise.	LOW	STRONG
4. In a Sjögren's patient with ILD, a surgical lung biopsy is not routinely recommended. A lung biopsy may be considered following a multidisciplinary review where a biopsy may have significant management implications, such as in: • Neoplastic and non-neoplastic lymphoproliferative disorder • Other cancers • Amyloid • Progressive deterioration and a suspected infection failing empiric therapies where less invasive testing proved nondiagnostic	INTERMEDIATE	STRONG
5. If a Sjögren's-ILD patient is asymptomatic for lung disease or demonstrates minimal impairment on PFTs or HRCT, serial monitoring by PFTs is recommended every 3-6 months to establish disease trajectory and initiation of pharmacotherapy only if serial studies document a significant decline in lung function.	INTERMEDIATE	STRONG
Recommendations: ILD—nonpharmacological and other management		
1.Vaccination: All Sjögren's patients must be immunized against influenza and pneumococcal infection (Prevnar and Pneumovax) in accordance with Centers for Disease Control and Prevention guidelines.	HIGH	STRONG
2.Pneumothorax and cystic lung disease: Because a Sjögren's patient with cystic lung disease might have an increased risk of pneumothorax, patients and caregivers/family must be educated about signs and symptoms of pneumothorax and instructed to seek immediate medical attention if they experience signs or symptoms.	INTERMEDIATE	STRONG
3. Pulmonary rehabilitation and ILD: In a symptomatic Sjögren's patient with ILD and impaired pulmonary function, referral for pulmonary rehabilitation is recommended.	INTERMEDIATE	STRONG
4. Oxygen and ILD: In a Sjögren's patient with suspected ILD and clinically significant resting hypoxemia (defined by resting oxygen saturation $< 88\%$, $Pa_{O_2} < 55$ mm Hg or < 60 mm Hg with complication of chronic hypoxemia such as cor pulmonale), long-term oxygen therapy is recommended.	INTERMEDIATE	STRONG
5A. Air travel and ILD: In a Sjögren's-ILD patient considering air travel, the need for supplemental oxygen should be evaluated by a physician.	INTERMEDIATE	MODERATE
5B. Air travel and ILD: In a Sjögren's patient with ILD, discouraging air travel is not recommended unless the patient develops signs and symptoms of pneumothorax or new onset/unexplained chest pain or dyspnea prior to boarding.	INTERMEDIATE	STRONG
6. Lung transplant and ILD: In a Sjögren's patient with ILD whose condition is advanced with resting hypoxia or whose lung function is rapidly deteriorating, lung transplant evaluation is recommended.	INTERMEDIATE	STRONG
Recommendations: ILD—pharmacological interventions		
1A. Symptomatic/moderate-severe ILD—systemic corticosteroids: In Sjögren's patients with symptomatic ILD with moderate to severe impairment on lung function, imaging, or in gas-exchange and especially in organizing pneumonia, systemic steroids should be considered as a first-line treatment at	INTERMEDIATE	MODERATE

(Continued)

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TABLE 4] *(Continued)*

Recommendation	Strength of Evidence	Strength of Recommendation
a dosage based on the clinical context and disease severity, with standard dosage being 0.5-1.0 mg/kg.		
1B. Cautions for systemic corticosteroids: In a Sjögren's patient with ILD or a related disorder, providers must be aware of the following risks/potential harms: Potential short-term side effects[a]: • Glucose intolerance • Avascular necrosis • Mineralocorticoid effect, leading to potential fluid retention and/or hypertension • Myopathy • Psychological, including hyperactivity, insomnia, psychosis • Pancreatitis • Hypertension • Truncal obesity • Acne • Hematopoietic, including leukocytosis • Ecchymosis • Acanthosis nigricans Potential long-term side effects: • Osteoporosis • Diabetes • Adrenal insufficiency • GI symptoms, including peptic ulcer, hepatic steatosis • Ophthalmological, including glaucoma, cataract • Hyperlipidemia • Congenital malformation in utero exposure (very rare) • Growth suppression (only in pediatrics)	HIGH	STRONG
2A. Symptomatic/moderate-severe ILD—MMF or azathioprine: In a Sjögren's patient with symptomatic ILD with moderate to severe impairment as determined by lung function testing, imaging, or gas-exchange, MMF or azathioprine should be considered when long-term steroid use is contemplated and steroid-sparing immunosuppressive therapy is required.	INTERMEDIATE	MODERATE
2B. Cautions for azathioprine: In a Sjögren's patient with ILD or related disorder and considering use of azathioprine, patients and health-care providers must be aware of potential risks for drug-induced pneumonitis, GI upset, hepatotoxicity, bone marrow suppression, rash, and hypersensitivity syndrome. Testing for thiopurine methyltransferase activity or genotype before initiating azathioprine is recommended to reduce the risk of severe, life-threatening leukopenia due to complete lack of thiopurine methyltransferase activity.[a]	HIGH	STRONG
2C. Cautions for MMF: In a Sjögren's patient with ILD or related disorder and considering use of MMF, patients and health-care providers must be aware of potential side effects, including nausea, diarrhea, hepatotoxicity, and bone marrow suppression.[a]	HIGH	STRONG
1. Symptomatic/moderate-severe ILD—maintenance therapies: Following initial treatment for Sjögren's patients with ILD who are symptomatic and in whom PFTs or HRCT demonstrated moderate-severe impairment, first-line maintenance drugs should be either MMF or azathioprine.	LOW	MODERATE
4A. Symptomatic/ moderate-severe ILD—second-line therapies: If initial treatment with MMF or azathioprine is insufficient or not tolerated in Sjögren's patients with ILD who are symptomatic and in whom PFTs or HRCT demonstrated moderate-severe impairment, subsequent second-line maintenance drugs may include rituximab and calcineurin inhibitors, cyclosporine, or tacrolimus.	LOW	WEAK
4B. Cautions for rituximab: In a Sjögren's patient with ILD considering use of rituximab, patients and health-care providers must be aware of the following potential risks/harms, although rare[a]:	HIGH	STRONG

(Continued)

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TABLE 4] *(Continued)*

Recommendation	Strength of Evidence	Strength of Recommendation

• Pneumonitis
• Worsening of ILD
• Infusion reactions
• Tumor lysis syndrome in those with NHL
• Bacterial, viral, or fungal infections including:
  • Hepatitis B reactivation with possible fulminant hepatitis
  ○ Progressive multifocal leukoencephalopathy
• Hypogammaglobulinemia
• Cytopenias
• Severe mucocutaneous reactions
• Bowel obstruction and perforation
• Cardiac arrhythmias and angina
• In pregnancy and nursing, risk vs benefit must be carefully considered
• Avoid live vaccines with rituximab		

5.Symptomatic/moderate-severe Sjögren's-ILD—antifibrotic drugs[b]: The use of antifibrotic therapy such as nintedanib should be tried as a second-line maintenance therapy either alone or in combination with immunomodulatory agents in Sjögren's patients with progressive fibrotic ILD who are symptomatic and in whom PFTs or HRCT demonstrated moderate-severe impairment**.**	LOW	MODERATE
6.Rapidly progressive or exacerbating ILD—IV steroids: In Sjögren's patients with ILD who are rapidly progressive or present with acute respiratory failure, a trial of high-dose corticosteroids (such as IV methylprednisolone) is recommended. Alternative etiologies, such as infections or lymphoproliferative disorders, must be considered.	INTERMEDIATE	STRONG
7A. Symptomatic/refractory, rapidly progressive, or exacerbating ILD—cyclophosphamide: In a Sjögren's patient with ILD who has acute or subacute hypoxic respiratory failure requiring hospitalization, despite initial therapies, rituximab or cyclophosphamide should be considered in addition to high-dose corticosteroids.	LOW	MODERATE
7B. Cautions for cyclophosphamide: In Sjögren's with ILD when cyclophosphamide is considered, the significant risks must be assessed[a] and *Pneumocystis jirovecii* prophylaxis provided. Risk of bladder cancer can be greatly reduced with IV vs oral route.	INTERMEDIATE	STRONG
8. Drug-induced lung disease: Clinicians and patients must be aware of pulmonary complications associated with medications used in Sjögren's and related CTDs, particularly when patients are progressive or refractory to therapies. Complications may include infections, malignancies, bronchospasm, and drug-induced ILD, and may require bronchoscopy, biopsy, and/or withdrawal of the medication. In addition to medication withdrawal, corticosteroids may be used if significant symptoms and respiratory impairment are present. While the risk is low for most agents (approximately 1%), health-care providers should keep in mind that medications used to treat Sjögren's have been associated with drug-induced ILD, including: • TNF-alpha inhibitors • Sulfasalazine • Cyclophosphamide • Rituximab • Leflunomide • Methotrexate • Sulfonamides	INTERMEDIATE	STRONG

CTDs = connective tissue diseases; HRCT = high-resolution CT; ILD = interstitial lung diseases; MMF = mycophenolate mofetil; NHL = non-Hodgkin lymphoma; PFTs = pulmonary function tests; TNF = tumor necrosis factor.

[a]Refer to the US Food and Drug Administration label for additional information.

[b]The antifibrotic, nintedanib, was US Food and Drug Administration-approved for progressive fibrotic ILD just as these recommendations went to consensus. This factor, in addition to the authors' awareness of minimal experience with antifibrotics in autoimmune disease, precluded inclusion of a Recommendation listing cautions for antifibrotics. Please consult the PDR for potential risks and side effects. Q27

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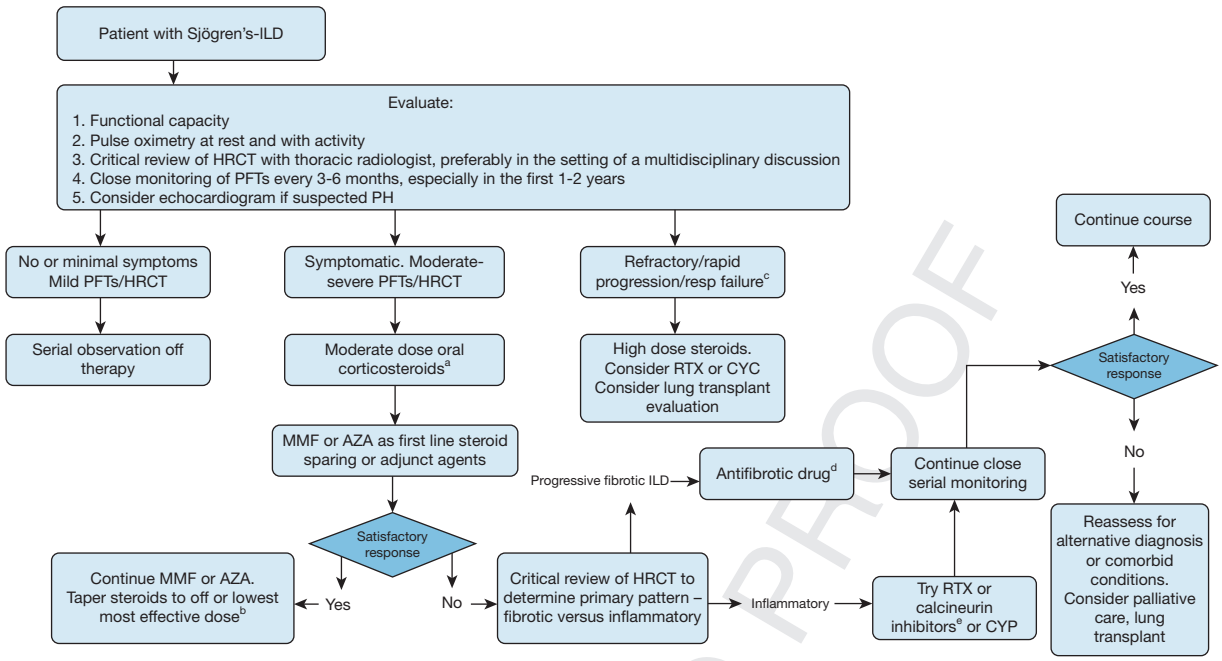

Figure 3 – *Evaluation and management of patients with Sjögren's who exhibit symptoms and/or physical examination signs of interstitial lung disease. Details regarding PFTs and HRCT examinations are given in Figure 1.* [a]*The dose and duration of corticosteroids in Sjögren's-ILD is not standardized. The panel proposes a dose not to exceed 60 mg daily of prednisone with a slow taper over weeks-months. In rapidly progressive ILD, or acute respiratory failure, consider pulse dose IV corticosteroids or high-dose oral corticosteroids up to 60 mg daily of prednisone.* [b]*In patients who are not able to successfully taper off corticosteroids, or experience unfavorable adverse effects, or in patients where the length of corticosteroid therapy is predicted to be long-term, steroid-sparing agents should be initiated as maintenance therapy.* [c]*Condition rapidly deteriorates and requires hospitalization.* [d]*Nintedanib is approved by the US Food and Drug Administration for progressive fibrotic lung disease phenotype.* [e]*Calcineurin inhibitors can be considered in patients who are intolerant to the initial maintenance therapy; no evidence to support the superiority in patients who fail the first-line therapy. AZA = azathioprine; CYP = cyclophosphamide; HRCT = high-resolution CT; ILD = interstitial lung disease; MMF = mycophenolate mofetil; PFTs = pulmonary function tests; PH = pulmonary hypertension; RTX = rituximab.*

Sjögren's-ILD, TRG members typically perform full PFTs at the time of the initial evaluation followed by repeat assessment every 3 to 6 months, especially in the first 1 to 2 years. The frequency of subsequent testing is dictated by an individual patient's pace of disease progression.

Many of the pharmacological interventions are based on the severity of the Sjögren's-ILD. While no standard definition exists for staging, the panel bases severity on the pulmonary domain disease activity defined by EULAR Sjögren's Syndrome Disease Activity Index, which uses symptoms defined by the New York Heart Association (NYHA) Functional Classification, imaging, and PFT results.[34] In general, moderate and severe/high disease activity is gauged as follows:

- Moderate: shortness of breath on exercise (NYHA II) or PFTs restricted to FVC between 60% and 80% predicted or D_{LCO} between 40% and 70% predicted.
- Severe/high: shortness of breath at rest (NYHA III, IV) or PFTs with FVC < 60% predicted or D_{LCO} < 40% predicted.

Close follow-up is required for all pharmacological treatments. Additionally, the TRG and CEP recognized the paucity of specific clinical trials dedicated to Sjögren's-ILD as a significant and high priority research gap. The recommendations (Table 4) and the clinical pathway (Figure 3) are based on extrapolation of current guidelines and literature on non-Sjögren's ILD, including important recent clinical trials on the potential role of antifibrotic therapies (eg, nintedanib) in CTD-ILD.[35]

Therapies reported for Sjögren's-ILD along with their mechanism of action, common side effects, and level and strength of recommendation are summarized in e-Appendix 7. Nintedanib, an antifibrotic, was recently approved for "progressive" fibrotic ILD phenotypes, which may also include those associated with Sjögren's and other CTDs. Common side effects include diarrhea or loose stools and GI upset, the former commonly treated with loperamide. Medication monitoring involves assessing for drug-induced liver injury with baseline and serial evaluation of transaminases and total bilirubin.

TABLE 5] Recommendations for Lymphoproliferative Disease in Sjögren's Patients

Diagnosis, Evaluation and Management for Lymphoproliferative Disease in Sjögren's Patients	Strength of Evidence	Strength of Recommendation
1. The possibility of lymphoma must be further investigated in a Sjögren's patient with symptoms such as unexplained weight loss, fevers, night sweats, and/or the presence of head and neck lymphadenopathy and/or parotitis.	HIGH	STRONG
2. All Sjögren's patients must be clinically monitored for signs and symptoms of pulmonary lymphoproliferative disorders, including lymphoma and amyloid.	HIGH	STRONG
3. In Sjögren's patients suspected of having lymphoproliferative complications, a HRCT chest scan should be considered more appropriate than a baseline CXR at the time of initial diagnosis.	INTERMEDIATE	MODERATE
4. In a Sjögren's patient with pulmonary lesions (nodules > 8 mm, consolidations, or lymphadenopathy) in whom a neoplasm is suspected, a PET scan should be considered.	INTERMEDIATE	MODERATE
5. In Sjögren's patients with lymphadenopathy, growing lung nodules, and/or progressive cystic lung disease, a biopsy should be recommended. Clinical and radiographic observation may be appropriate in select patients with incidental subcentimeter nodules, stable cysts, and isolated PET-negative subcentimeter lymphadenopathy.	INTERMEDIATE	MODERATE
6. In a Sjögren's patient in whom a neoplasm has been confirmed or suspected, multidisciplinary review involving rheumatologist/primary care physician, pulmonologist, pathologist, radiologist, and hematologist/oncologist is recommended.	LOW	STRONG

CXR = chest radiograph; HRCT = high-resolution CT.

Lymphoproliferative Disease

Six recommendations were developed on lymphoproliferative disease in Sjögren's (Table 5). Concerns for lymphoma development in Sjögren's, which ranges from 5% to 18%, are delineated in numerous papers.[38-42] Lymphoproliferative involvement of the lungs can present as non-resolving consolidations, focal nodules (particularly in the presence of parotitis), lymphadenopathy, and cystic lesions accompanied by adjacent nodules and may be asymptomatic.

Examination findings of importance include lymphadenopathy and parotitis, particularly when PET-avid parotitis (standardized uptake value $\geq$ 4.7) is accompanied by lung nodules.[43,44] Focal lung nodules and consolidations are present in approximately one-third of Sjögren's patients with pulmonary lymphoma vs 3% without lymphoma.[43] Multiple sub-centimeter lung nodules accompanied by adjacent cystic lesions (typically < 1 cm in size in peribronchovascular and subpleural distributions) may further indicate a MALT lymphoma with focal amyloidosis.[45] Presence of ILD does not appear to indicate a higher risk for lymphoma.[43]

Sjögren's patients are at a higher risk for both non-neoplastic (eg, nodular lymphoid hyperplasia, follicular bronchiolitis, lymphoid interstitial pneumonia) and neoplastic monoclonal lymphoproliferative disorders. Approximately 6% of Sjögren's-associated lymphomas may directly involve the lungs and are most commonly of the MALT type, manifesting as focal nodules, consolidations, and/or masses.[32,43,46] Cystic lesions in the lungs due to amyloid involvement can be associated with Sjögren's, as well as MALT lymphomas and are highly suggestive of Sjögren's.[45] Given the prevalence and increased risk for lymphoproliferative disorders, active clinical surveillance for pulmonary lymphoproliferative complications in Sjögren's is recommended, especially for Sjögren's patients who are at high risk for lymphoma. Known risk factors include persistent salivary gland swelling, vasculitis and palpable purpura, lymphadenopathy, laboratory findings of low complements (C3 or C4), monoclonal gammopathy, cryoglobulins, anti-SSA (or Ro) and/or anti-SSB (or La), rheumatoid factor, anemia, leukopenia, lymphopenia, neutropenia, thrombocytopenia, elevated serum beta$_2$-microglobulin, and/or B-cell activating factor.[41]

HRCT and PET scan abnormalities are common in Sjögren's with or without lymphomatous complications.[7,43] Multidisciplinary review with oncology can aid in diagnosis and management. MALT lymphomas as well as cystic lung disease associated with Sjögren's often have an indolent course and can be managed conservatively.[27,28,47] Frequency of HRCT monitoring will be variable

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based on cyst size/appearance and clinical presentation. Accessibility to PET, costs, and insurance coverage should be considered. Many US clinicians may have difficulty obtaining payor authorization for a PET scan if it is not ordered by an oncologist or if malignancy is not yet diagnosed by histopathologic confirmation.

Conclusions

Pulmonary involvement due to Sjögren's is common and frequently involves upper and lower airways disease, parenchymal or interstitial lung disease, and associated lymphoproliferative disease. A common theme for all of these recommendations, and endorsed by the TRG, is the need for a multidisciplinary approach in the care of Sjögren's patients with suspected or confirmed pulmonary complications, including a rheumatologist, primary care physician, pulmonologist, pathologist, radiologist, and, when appropriate, an oncologist.

While most of the evidence would be considered of low quality due to the lack of randomized, placebo-controlled clinical trials, our recommendations and strength of the recommendations incorporate Sjögren's-specific expertise in pulmonology, rheumatology, and hematology/oncology. Thirty-four recommendations were rated as strong, indicating the extent of agreement that these recommendations reflect best practice, while 11 were rated as moderate and six as weak. The lowest level of agreement for any recommendation was 79% for the weak recommendation to consider performing PFTs to detect underlying pulmonary manifestations in asymptomatic Sjögren's patients. CEP comments primarily cited the burden and expense of obtaining PFTs as well as an improbability of non-pulmonologists ordering such tests due to inadequate awareness of and appreciation for pulmonary manifestations in Sjögren's. Overall, the CEP provided a high level of agreement for the recommendations and strength of the recommendations, with 76 of the 102 questions provided for voting receiving higher than 98% agreement.

Clinical practice guidelines for pulmonary manifestations in Sjögren's may improve early identification, evaluation, and uniformity of care by primary care physicians, rheumatologists, and pulmonologists. Full clinical rationales and references developed by the TRG for these recommendations may be viewed in e-Appendix 5. The guidelines process also has led to identification of high priorities for future research (e-Appendix 8). These priorities include epidemiological and risk analyses, blood-based and noninvasive biomarkers, quantitative imaging tools, optimal frequency of repeat PFTs and HRCT testing for each pattern of pulmonary disease, studies on etiology and treatment, and specifically on antifibrotics for Sjögren's-ILD.

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Additional information: The e-Appendixes can be found in the Supplemental Materials section of the online article. A full list of references is available in e-Appendix 9.

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