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Non-IPF Interstitial Lung Disease Therapeutic Options

An APCCMPD Ambulatory Care Curriculum Teaching Script

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Non-IPF Interstitial Lung Disease Therapeutic Options

Scenario 1:

A 43-year-old man presented with 6 months of progressive dyspnea on exertion without associated cough, fevers, chills, chest pain, join pains, skin changes, abdominal pain, nausea, or diarrhea. He has had 10 lbs. weight loss in the last 6 months. He was previously healthy and denies any prior surgeries. He currently takes no medications. He is married with 2 children. He works in an auto body shop but does not have any contact with brakes. He denies any asbestos exposure or dust fumes. His occupational history is also notable for prior minimal work in sandblasting, farming, and construction. He is a lifetime non-smoker. He denies any use of drugs or alcohol. There is no family history of lung disease. His exam is notable for shallow respirations and bibasilar crackles. He has negative autoimmune serologies and a negative hypersensitivity panel. He undergoes bronchoscopy with BAL that is negative for PCP and shows a lymphocytosis. He ultimately undergoes a VATS biopsy that is consistent with nonspecific interstitial pneumonitis (NSIP).

Notable testing:

Pulmonary function tests (PFT):
Forced Expiratory Volume in 1 second (FEV1) of 1.67 (54% predicted)
Forced Vital Capacity (FVC) 1.78 (50% predicted)
Diffusing capacity of the lungs for carbon monoxide (DLCO) 45% predicted
6-minute walk test: Oxygen saturation of 91% on room air at rest and requires 2LPM with exertion.
Imaging is shown below in Figure 1.

Figure 1. CT Scan Chest

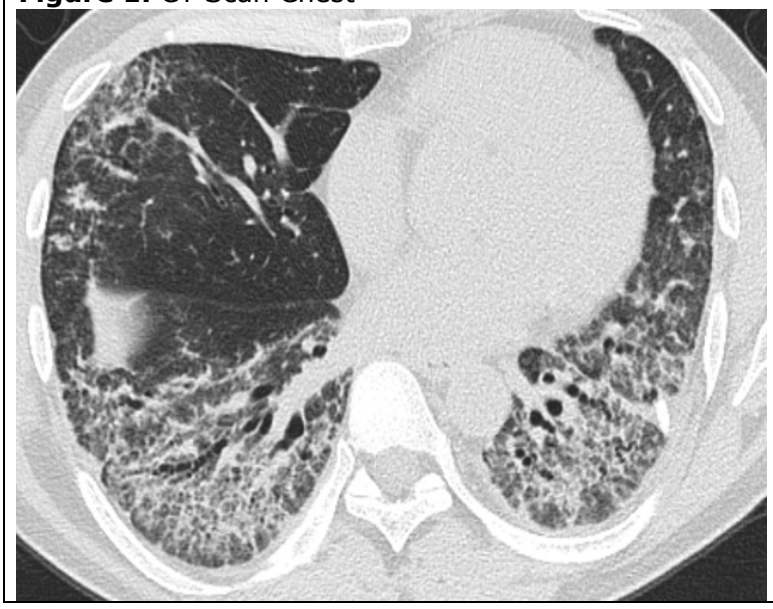

Image borrowed from Travis et al (AJRCCM 2006)

Question 1: What are the treatment options for this patient with NSIP?

Question 2: What are some steroid sparing agents to consider for treating NSIP?

Question 3: The patient achieves improvement with prednisone. His symptoms worsened when attempting to wean prednisone and the decision is made to start him on mycophenolate mofetil. He achieves stability in his FVC and DLCO for 14 months, but he later returns for follow-up with worsening dyspnea, hypoxemia with exertion, and worsening pulmonary function. You repeat a high-resolution CT chest that shows progression of fibrosis. How would these findings change your management?

Scenario 2:

A 50-year-old man who was otherwise well presents for evaluation of breathlessness with exertion, hand swelling, dry hands with cracking, and Raynaud's phenomenon. He was well until a month ago, when he developed joint pain and fatigue. His physical exam was notable for Gottron's papules, fissuring of his fingertips, facial erythema, and shawl sign. His HRCT is shown in Figure 2.

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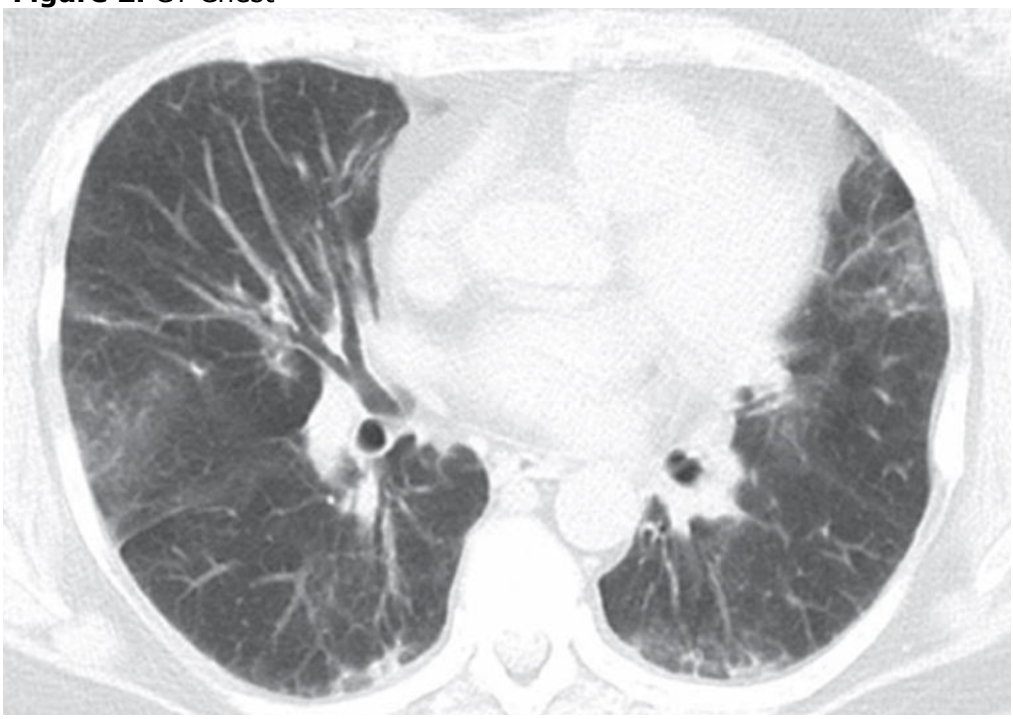


Images borrowed from Solomon, et al. (Jornal Brasiliero de pneumologia, 2011).

After review at your multidisciplinary interstitial lung disease conference, the radiologic pattern is determined to be NSIP. He was ultimately diagnosed with dermatomyositis and, thus, CTD-ILD.

His PFTs are notable for moderate restriction with FEV1 62% predicted, DLCO 55% predicted. His ambulatory saturation nadir on his 6MWT was 93% on room air.

Question 4: What are the treatment options for ILD related to myositis?

Scenario 2 (Continued):

The patient returns for follow up with progressive dyspnea, but CT chest shows stability in lung disease. Repeat pulmonary function is stable, except DLCO has declined significantly. You obtain an echocardiogram that shows new right ventricle (RV) failure with an elevated estimated pulmonary artery systolic pressure.

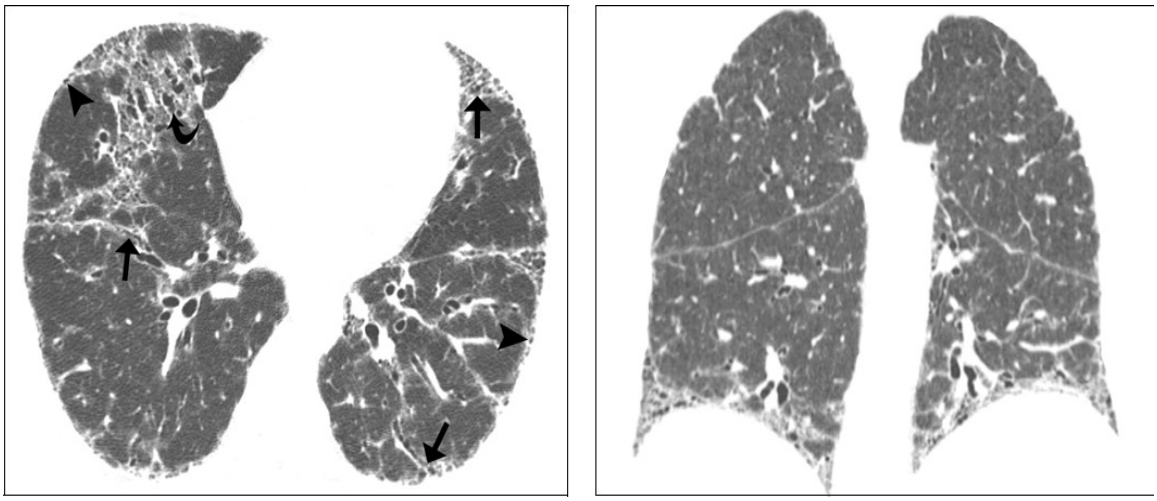
Question 5: While this patient may have combined Group 1 (CTD) and Group III (ILD) pulmonary hypertension, what therapeutic options should be considered for pulmonary hypertension related to ILD?

Question 6: What are treatment options for systemic sclerosis-related ILD (SSc-ILD)?

Scenario 3:

A 65-year-old woman presents with shortness of breath and cough. She had a CXR and was told that she had a viral infection. However, her symptoms persisted, so she had another CXR and HRCT (see images below). She was diagnosed with IPF with moderate restriction and started on pirfenidone. When she presents to you for a second opinion months later, she feels much better. She tells you that she owns a plant nursery, and her symptoms are temporally associated with peat moss deliveries. She undergoes surgical lung biopsy that demonstrates extensive interstitial fibrosis and patchy inflammation, numerous fibroblast foci and non-necrotizing granulomas in a bronchovascular distribution, most prominent in the upper lobes. These features are suggestive of hypersensitivity pneumonitis. Her imaging is demonstrated in Figure 4.

Figure 4. CT Chest



Images borrowed from Silva CI, et al. AJR 2007.

Question 7: What factors do you consider in the diagnosis of hypersensitivity pneumonitis (HP)?

Question 8: What are the therapeutic options for management of hypersensitivity pneumonitis (HP)?

Question 9: For patients on long-term corticosteroid therapy, when should you start pneumocystis prophylaxis?

Non-IPF Interstitial Lung Disease Therapeutic Options

Educational Objectives:

1. Describe the medical treatment options for various interstitial lung diseases
2. Review drug initiation and monitoring
3. Discuss additional non-pharmacologic therapeutic considerations

Scenario 1:

A 43-year-old man presented with 6 months of progressive dyspnea on exertion without associated cough, fevers, chills, chest pain, join pains, skin changes, abdominal pain, nausea, or diarrhea. He has had 10 lbs. weight loss in the last 6 months. He was previously healthy and denies any prior surgeries. He currently takes no medications. He is married with 2 children. He works in an auto body shop but does not have any contact with brakes. He denies any asbestos exposure or dust fumes. His occupational history is also notable for prior minimal work in sandblasting, farming, and construction. He is a lifetime non-smoker. He denies any use of drugs or alcohol. There is no family history of lung disease. His exam is notable for shallow respirations and bibasilar crackles. Imaging is shown below in Figure 1.

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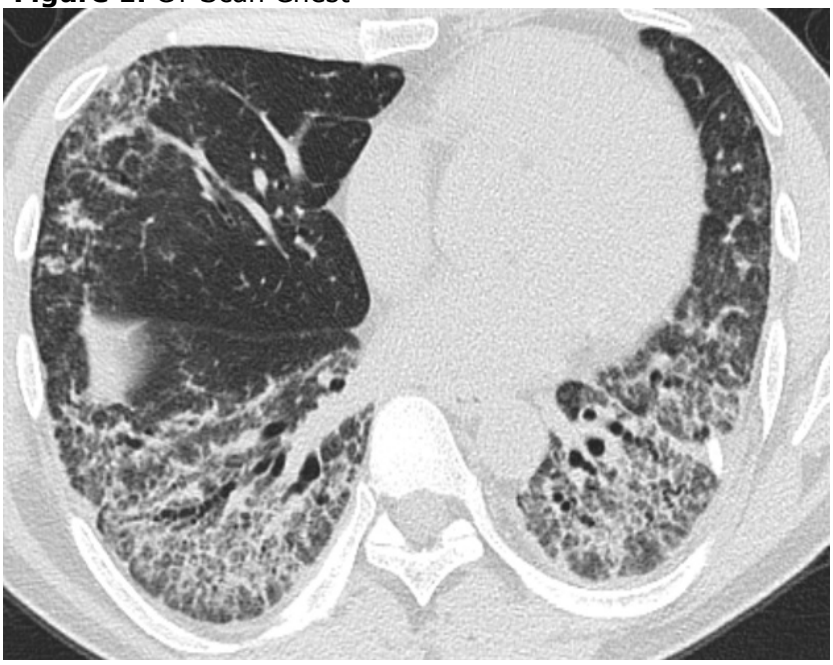

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Diffusing capacity of the lungs for carbon monoxide (DLCO) 45%
6-minute walk test: Oxygen saturation of 91% on room air at rest and requires 2LPM with exertion.

He has negative autoimmune serologies and a negative hypersensitivity panel. He undergoes bronchoscopy with BAL that is negative for PCP and shows a lymphocytosis. He ultimately undergoes a VATS biopsy that is consistent with nonspecific interstitial pneumonitis (NSIP).

Question 1: What are the treatment options for this patient with NSIP?

This patient has a clinical diagnosis of idiopathic NSIP (iNSIP) rather than NSIP in the context of connective tissue disease or a specific exposure. To date, clinical trials evaluating the efficacy of treatment for idiopathic NSIP have been limited. The standard practice is guided by clinical experience and small retrospective studies, many of which included non-idiopathic NSIP cases. Clinicians should be sure that their work-up for connective tissue diseases and potential exposures is complete in any case of NSIP where an underlying cause is not immediately evident.

For patients with moderate to severe disease (symptomatic and/or requiring supplemental oxygen), initial treatment with corticosteroids has been the mainstay of treatment. Usual daily dosing in clinical practice ranges 0.5-1 mg/kg of prednisone for ideal body weight. In patients with severe hypoxemia, such as those requiring high flow oxygen or intubation, some clinicians favor a pulse dose of methylprednisolone (typically 1 gram daily for three days) as an induction before switching to prednisone.

After approximately 4-6 weeks, steroids are slowly tapered. A steroid-sparing agent can be initiated once a definite response to corticosteroids has been established. In patients who do not achieve any benefit from weeks of corticosteroid therapy, the role of ongoing immunosuppression should be reconsidered. In patients with progressive fibrotic ILD, antifibrotic therapy should be added.

Question 2: What are some steroid sparing agents to consider for treating NSIP?

Studies regarding best treatment options in NSIP are limited and mostly small case series. The only randomized clinical trial to include patients with iNSIP was the recently published EVER-ILD trial (Mankikian et al, ERJ 2023), in which 43 of the total 122 randomized patients had iNSIP. Subjects were randomized to mycophenolate plus placebo or mycophenolate and rituximab with outcomes favoring combination therapy.

Preference for steroid-sparing agents will vary by practice. Preferred agents come from extrapolation of experience in well-defined connective tissue disease interstitial lung disease (ILD), especially scleroderma and myositis spectrum conditions, such as with mycophenolate, azathioprine, rituximab, and cyclophosphamide.

Commonly used steroid-sparing agents and their characteristics are summarized in Table 1.

Table 1. Immunosuppressants Used in the Treatment of Idiopathic NSIP.

Drug	Dosing	Baseline Labs	Safety Monitoring Labs	Side Effects	Time to Expected Therapeutic Effect
Mycophenolate mofetil (CellCept), mycophenolate sodium (Myfortic)	Start at 500 mg BID and increase every 2 weeks by 500 mg BID (max dose 1.5g BID) *Mycophenolate mofetil 500 mg = mycophenolate sodium 360 mg (max 720mg BID)*	CBC, CMP	CBC and CMP every 2-4 weeks for 3 months, then every other month thereafter	GI upset, marrow suppression, infection, PML, malignancy; avoid during pregnancy/lactation	~3 months

Azathioprine (Imuran)	2-3 mg/kg daily; start at 50 mg and increase every 1-4 weeks by 50 mg daily (max dose 150-200 mg daily)	CBC, LFT, TMPT*	CBC and LFT - every 2-4 weeks for 3 months, then every other month thereafter	Abnormal LFTs, leukopenia, GI upset, flu-like symptoms, pancreatitis, hypersensitivity, infection, malignancy	~3 months
Cyclophosphamide (Cytoxan)	Variable, recommend 500-750 mg/m2 monthly, oral 2mg/kg/day	CMP, CBC, UA	CBC, CMP, and UA 10 - 14 days post infusion	Abnormal LFTs, leukopenia, cystitis and bladder cancer, infection, GI upset, gonadal toxicity, infertility, malignancy	~2-3 months
Rituximab (Rituxan, Ruxience, Truxima, Riabni)	1 g on days 0 and 14, repeat every 6 months	HIV, Hepatitis B surface antigen and core antibody, hepatitis C antibody, Quantiferon Gold	CBC, CMP before each dose	Infusion reactions, hepatitis B reactivation, hypogammaglobulinemia and infection, progressive multifocal leukoencephalopathy, arrhythmias, skin rash, hypophosphatemia, abdominal pain	~2-3 months

CBC: complete blood count; CMP: comprehensive metabolic panel; LFT: liver function tests; TPMT: thiopurine methyltransferase; UA: urinalysis
**Not all practitioners check TMPT level prior to starting and choose to titrate dose per monitoring (See as an example of clinical discussion: Coenen et al.* Gastroenterology *149 (4): P907-917.)*
Typical dosing, safety monitoring, and side effect concerns with specific agents.

Question 3: The patient achieves improvement with Prednisone. His symptoms worsened when attempting to wean prednisone and the decision is made to start him on mycophenolate mofetil. He achieves stability in his FVC and DLCO for 14 months, but he later returns for follow-up with worsening dyspnea, hypoxemia with exertion and worsening pulmonary function. You repeat a high-resolution CT chest that shows progression of fibrosis. How would these findings change your management?

In this patient with progressive fibrosis unresponsive to immunosuppression, antifibrotic therapy would be indicated. Nintedanib and nerandomilasthave been studied in progressive fibrotic lung disease in non-IPF patients in the INBUILD and FIBRONEER studies. Patients enrolled in the trial had to meet criteria for progression of ILD within 24 months prior to screening: a relative decline in the FVC of at least 10% of the predicted value, a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution CT, or worsening of respiratory symptoms and an increased extent of fibrosis. Patients who received Nintedanib or nerandomilast had a slower decline in forced vital capacity at 52 weeks compared to placebo o (Flaherty et al *NEJM*, 2019; Maher et al. *NEJM* 2025).

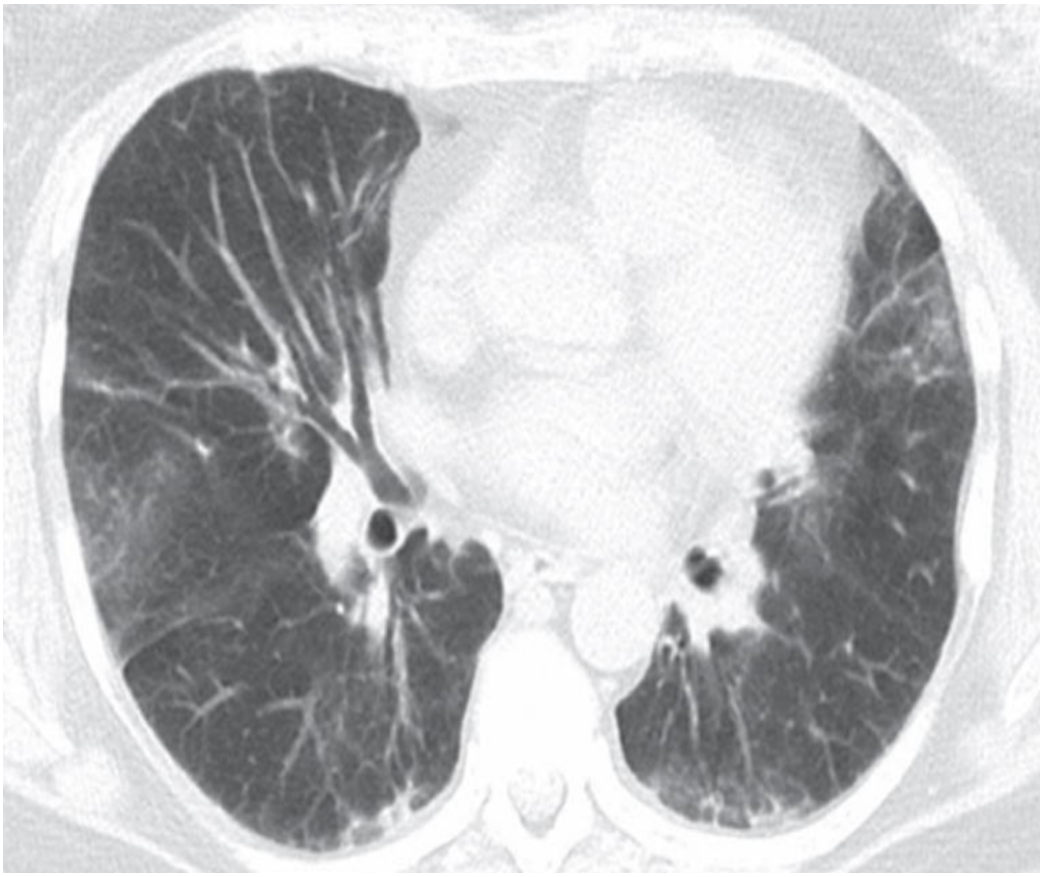
This patient should also be referred for transplant evaluation given progression of disease, age, and (presumed) single organ failure.

Question 4: What are the treatment options for ILD related to myositis?

Scenario 2:

A 50-year-old man who was otherwise well presents for evaluation of breathlessness with exertion, hand swelling, dry hands with cracking, and Raynaud's phenomenon. He was well until a month ago, when he developed joint pain and fatigue. His physical exam was notable for Gottron's papules, fissuring of his fingertips, facial erythema, and shawl sign. His HRCT is shown in Figure 2.

Figure 2. CT Chest



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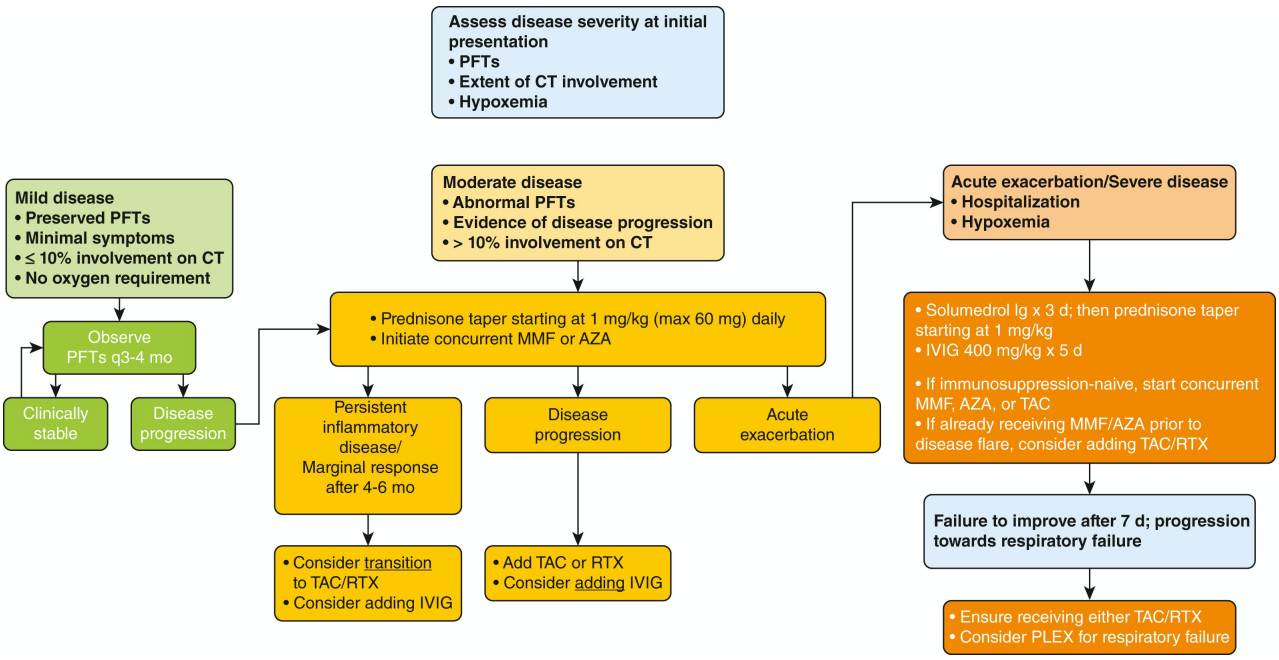
Regardless of radiographic or pathologic pattern, the first line treatment of ILD related to myositis is immunosuppression. The choice in agents is dictated by severity of illness and/or progression of disease on initial therapy. See Figure 3 for a proposed treatment approach for myositis-associated ILD (Hallowell & Danoff, *CHEST* 2023). Table 2 outlines additional therapeutic agents.

Figure 3. Treatment of Myositis-associated ILD



AZA: azathioprine; IVIG: intravenous immunoglobulin; MMF: mycophenolate; PLEX: plasma exchange; RTX: rituximab; TAC: tacrolimus
A proposed algorithm for approaching the treatment of myositis-associated ILD. (Hallowell & Danoff, Chest 2023)

Table 2. Immunosuppressants Used in Myositis-associated ILD (Not Covered in Table 1)

Drug	Dosing	Baseline Labs	Safety Monitoring	Side Effects	Time to Expected Therapeutic Effect
Tacrolimus	Start 0.5-1.0 mg bid; titrate to a trough of 5-10 ng/mL	CBC, CMP	CBC, CMP, tacrolimus trough every week fo the first month and every 4 weeks thereafter; lipid pane and yearly dermatology skin examination	Renal toxicity, hypertension, hyperlipidemia, tremors hyperglycemia, increased risk of malignancy	**~2-3 months**
IVIG	2 g/kg/mo divided over 3-5 d	Screen for IgA deficiency before initiation	N/A	VTE, volume overload, headaches (aseptic meningitis), antibody-mediated cytopenias, anaphylaxis, infusion reactions	**~1-2 months**

CBC: complete blood count; CMP: comprehensive metabolic panel; IgA: Immunoglobulin A; IVIG: intravenous immunoglobulin; VTE: venous thromboembolism.
Typical dosing, safety monitoring, and side effect concerns with specific agents.

A retrospective review of 125 patients with CTD-ILD was performed in patients treated with mycophenolate. Thirty-two of these patients had polymyositis or dermatomyositis. Patients with a non-UIP pattern had improvement in their FVC and DLCO and patients with CTD and UIP pattern had stability in their lung function (Fischer et al, J Rheumatology 2013).

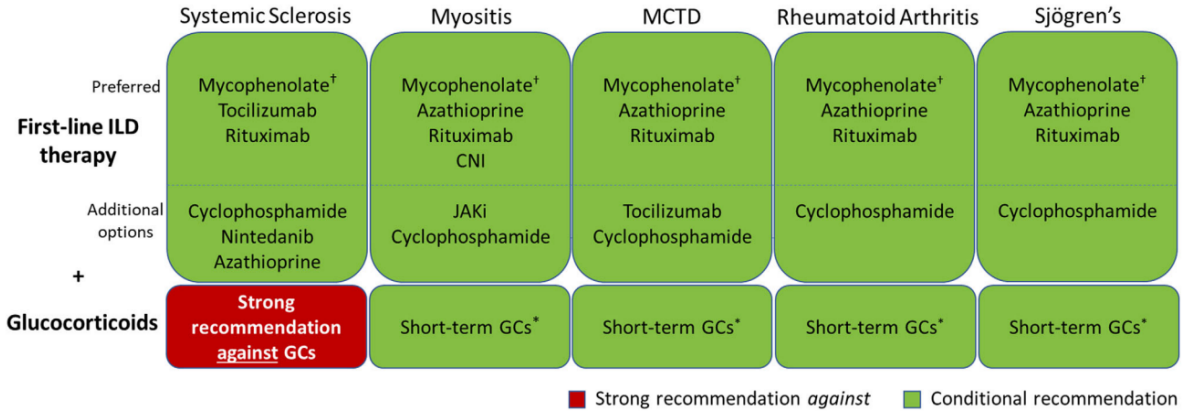
Azathioprine has been demonstrated to have similar efficacy based on case series (Marie et al, Arthritis Care Res 2013).

However, if patients are progressing despite first line therapy or presenting with more severe disease, there are further options including tacrolimus, rituximab, intravenous immunoglobulin (IVIG), and plasma exchange (PLEX).
Data to support the use of these medications are also derived from retrospective data or case series.

The phase 2b RECITAL trial (Maher et al, *Lancet Respir Medicine* 2023) randomized patients with severe or progressive CTD-ILD to cyclophosphamide versus rituximab. Of the 97 participants, 44 had myositis-associated ILD. Both agents had similar improvement in FVC from baseline and quality of life at 24 and 48 weeks. At 48 weeks, the change in FVC was+138 mL in cyclophosphamide v +112 mL in rituximab (p=0.345). Participants in the rituximab group had fewer adverse events and lower corticosteroid exposure over 48 weeks compared to the cyclophosphamide group.

A consensus guideline statement endorsed by American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) was published in 2024 with treatment guidelines for CTD-ILD (now increasingly referred to as Systemic Autoimmune Rheumatic Disease-ILD, or SARD-ILD). Given limited data, nearly all recommendations were conditional. These are summarized in Figure 4.

Figure 4. Initial Treatment Options for the Treatment of ILD Associated with SARD of Interest



CNI: calcineurin inhibitor; GC: glucocorticoid; ILD: interstitial lung disease; JAKi: JAK inhibitor; MCTD: mixed connective tissue disease; SSc: systemic sclerosis.
Preferred agents listed hierarchically per voting member consensus, though decisions regarding which agent to use may be driven by patient- or provider- specific factors. (Jonshon et al, Arthritis Rheumatol, 2024).

Scenario 2 (Continued):

The patient returns for follow up with progressive dyspnea, but CT chest shows stability in lung disease. Repeat pulmonary function is stable, except DLCO has declined significantly. You obtain an echocardiogram that shows new right ventricle (RV) failure with an elevated estimated pulmonary artery systolic pressure.

Question 5: While this patient may have combined Group 1 (CTD) and Group III (ILD) pulmonary hypertension, what therapeutic options should be considered for pulmonary hypertension related to ILD (PH-ILD)?

In patients with pulmonary hypertension due to interstitial lung disease, patients treated with inhaled treprostinil compared to placebo had an increase in 6-minute walk distance from baseline at week 16. Additionally, there was a significant reduction in NT-proBNP levels in patients treated with inhaled treprostinil compared to an increase in levels in the placebo group (Waxman et al. *NEJM* 2021). Emerging data also suggests that inhaled treprostinil reduces the rate of decline in FVC in PH-ILD, further supporting its use in these patients (Nathan et al. *NEJM* 2026).

Question 6: What are treatment options for scleroderma related ILD?

Several randomized controlled trials have evaluated therapy specifically in the scleroderma-ILD population:

Immunosuppression: Mycophenolate is the preferred initial immunosuppression.
SLS-1 (Tashkin, et al 2006) compared cyclophosphamide for 1 year vs. placebo and found an improvement in 2.5% of predicted FVC favoring cyclophosphamide, although the effect was lost once the drug was stopped.

SLS-2 (Tashkin, et al 2016) compared cyclophosphamide vs. mycophenolate mofetil. Both drugs had equal efficacy in improving FVC, dyspnea and skin thickness. However, cyclophosphamide was associated with greater withdrawal from the study due to side effects.

Antifibrotic therapy:
SENSCIS (Distler et al. *NEJM* 2019): compared nintedanib 150mg twice daily with placebo in patients diagnosed within last 7 years, with at least 10% fibrosis on HRCT. The annual rate of decline of FVC was lower in the nintedanib group compared to placebo– 52 mL vs 93 mL per year. This effect was more pronounced in the subgroup of patients who were not already on mycophenolate. Data from the FIBRONEER trial (Maher et al. *NEJM* 2025) also supports the use of nerandomilast in progressive pulmonary fibrosis of all kinds.

Early phase studies have assessed the use of pirfenidone in this patient population, though thus far more data is necessary (Khanna et al, J Rheum 2016; Khanna et al Arthritis Rheum 2022).

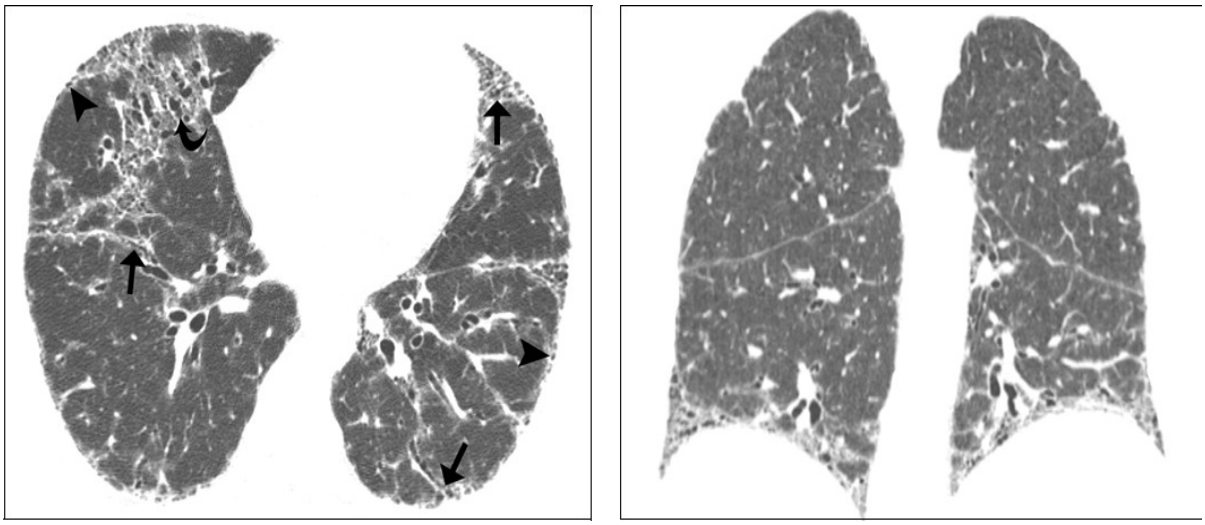
Biologic therapy:

FocuSSed (Khanna et al, Lancet Respiratory 2020): compared tocilizumab injections of 162 mg weekly vs. placebo Assessed the safety and efficacy of tocilizumab to treat skin fibrosis and systemic-sclerosis associated ILD. The tocilizumab group had less decline in FVC percent predicted at 48 weeks compared to placebo (14 mL vs 255 mL). There was no change in skin fibrosis with tocilizumab.

Scenario 3:

A 65-year-old woman presents with shortness of breath and cough. She had a CXR and was told that she had a viral infection. However, her symptoms persisted, so she had another CXR and HRCT (see images below). She was diagnosed with IPF with moderate restriction and started on pirfenidone. When she presents to you for a second opinion months later, she feels much better. She tells you that she owns a plant nursery, and her symptoms are temporally associated with peat moss deliveries. She undergoes surgical lung biopsy that demonstrates extensive interstitial fibrosis and patchy inflammation, numerous fibroblast foci and non-necrotizing granulomas in a bronchovascular distribution, most prominent in the upper lobes. These features are suggestive of hypersensitivity pneumonitis. Her imaging is demonstrated in Figure 5.

Figure 5. CT Chest



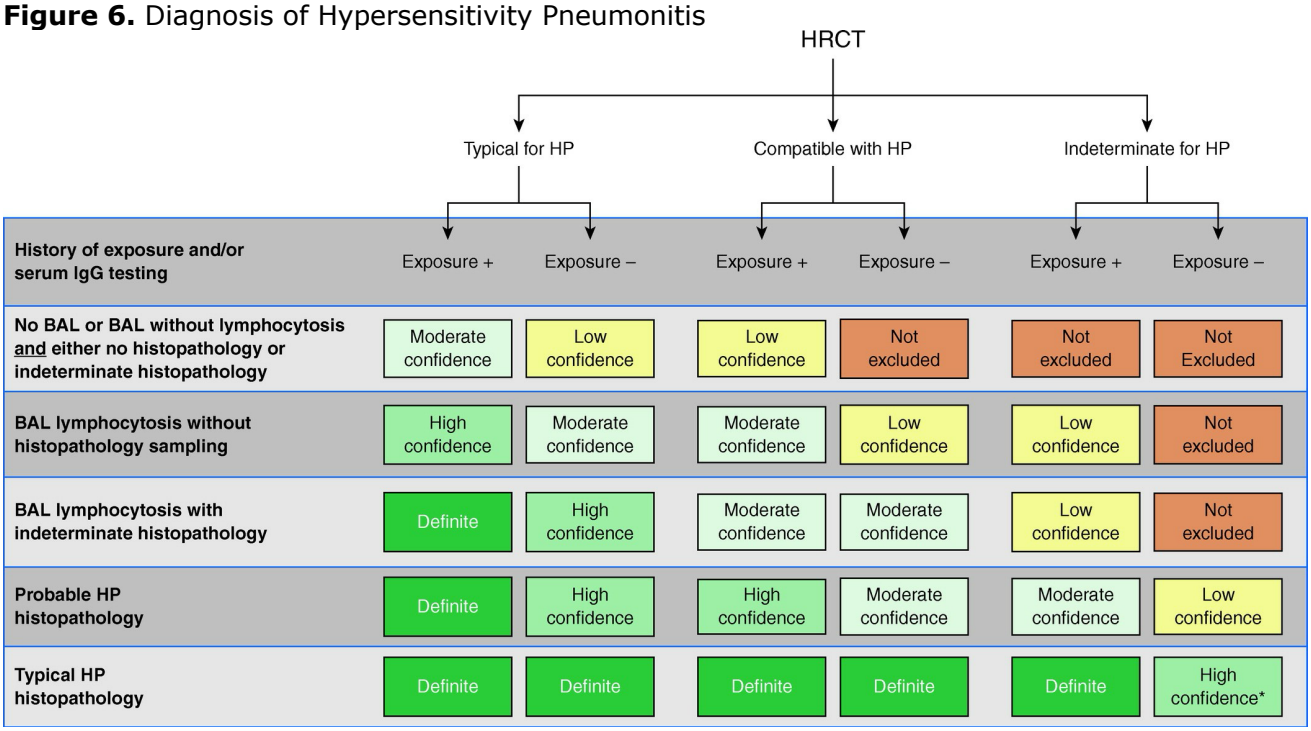
Images borrowed from Silva CI, et al. AJR 2007.

Question 7: What factors do you consider in the diagnosis of hypersensitivity pneumonitis (HP)?

There are now joint society clinical practice guidelines on the diagnosis of hypersensitivity pneumonitis. HP is classified as fibrotic or nonfibrotic (Raghu et al, *AJRCCM* 2020). Clinical factors to take into consideration for a diagnosis include the presence of an antigen associated with HP (bird dropping and feathers, molds, yeast, bacteria, etc.), HRCT pattern (mosaic attenuation, air trapping, three density pattern – previously referred to as "headcheese" pattern), bronchoalveolar lavage (BAL) lymphocytosis, and histopathologic findings of poorly formed granulomas.

The diagram in Figure 6 from the Clinical Practice Guideline referenced above combines clinical factors to ascribe levels of confidence to a clinical diagnosis of HP:

Figure 6. Diagnosis of Hypersensitivity Pneumonitis



History of exposure and/or serum IgG testing	Typical for HP: Exposure +	Typical for HP: Exposure –	Compatible with HP: Exposure +	Compatible with HP: Exposure –	Indeterminate for HP: Exposure +	Indeterminate for HP: Exposure –
No BAL or BAL without lymphocytosis and either no histopathology or indeterminate histopathology	Moderate confidence	Low confidence	Low confidence	Not excluded	Not excluded	Not Excluded
BAL lymphocytosis without histopathology sampling	High confidence	Moderate confidence	Moderate confidence	Low confidence	Low confidence	Not excluded
BAL lymphocytosis with indeterminate histopathology	Definite	High confidence	Moderate confidence	Moderate confidence	Low confidence	Not excluded
Probable HP histopathology	Definite	High confidence	High confidence	Moderate confidence	Moderate confidence	Low confidence
Typical HP histopathology	Definite	Definite	Definite	Definite	Definite	High confidence*

BAL= bronchoalveolar lavage; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography
Diagnosis of HP incorporates imaging, exposure assessment, BAL lymphocytosis, and histopathological findings. (Raghu et al, AJRCCM 2020)

Question 8: What are the therapeutic options for management of hypersensitivity pneumonitis (HP)?

Regardless of subtype of HP, the mainstay of therapy is removal of the antigen followed by thorough cleaning of the house or workplace.

In mild cases of nonfibrotic HP, removal of the offending antigen may be sufficient to reverse the injury. Patients with greater symptoms and/or hypoxemia can be treated with immunosuppression for reversal of inflammatory findings. For those patients that are treated, initial therapy involves corticosteroids at 0.5-1mg/kg, tapered over months. If patients cannot tolerate high dose corticosteroids, fail attempts at tapering, or do not respond to initial therapy, then steroid sparing agents can be considered.

There is greater uncertainty about the role of immunosuppression in fibrotic HP, particularly in the absence of inflammatory findings (BAL lymphocytosis, ground glass attenuation). In a retrospective review of 70 patients with HP, both mycophenolate and azathioprine were associated with increased DLCO after 1 year, although no improvement in FVC was seen (Morisset et al. CHEST, 2017). Other retrospective reports have also failed to demonstrate improvement in lung function with immunosuppression in fibrotic HP (Adegunsoye et al, Eur Respir J 2022). Furthermore, a large multicenter retrospective cohort analysis reported shorter survival in patients with fibrotic HP with short telomere length who received immunosuppression (Zhang et al., Eur Respir J 2023). The relevance of this to clinical care is limited by the fact that access to routine telomere length testing for clinical decision-making is limited by cost.

Question 9: For patients on long-term corticosteroid therapy, when should you start pneumocystis prophylaxis?

Typically, pneumocystis jirovecii pneumonia (PJP) prophylaxis should be initiated if patients are receiving prednisone 20 mg daily or more (or equivalent dosing of another corticosteroid) for greater than 3 weeks. For patients on another immunosuppressant in addition to prednisone, even if the prednisone dose is less than 20 mg daily, PJP prophylaxis should be considered. First-line therapy is with trimethoprim-sulfamethoxazole. Dapsone (if G6PD deficiency is excluded), atovaquone, or inhaled pentamidine are alternative regimens.

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