POSITION STATEMENT

Diagnosis and management of connective tissue disease-associated interstitial lung disease in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand*

ADELLE S. JEE,1,2,3 ROBERT SHEEHY,4,5 PETER HOPKINS,3,5,16 TAMERA J. CORTE,1,2,3 KAREN SYMONS,7 PAUL N. REYNOLDS,3,9,10 AND GREGORY J. KEIR4,5

LISA M. SPENCER,8 PAUL N. REYNOLDS,3,9,10 SALLY CHAPMAN,9 SALLY DE BOER,11 TARYN REDDY,12 ANNE E. HOLLAND,3,13,14,15 DANIEL C. CHAMBERS,3,14,16 IAN N. GLASPOLE,3,5,16 HELEN E. JO,1,2,3 JANE F. BLEASEL,2,18 JEREMY P. WROBEL,19,20 LEONA DOWMAN,3,13,21 MATTHEW J.S. PARKER,2,3,18 MARGARET L. WILSHER,3,11,22 NICOLE S.L. GOH,7,15,23,24 YUBEN MOODLEY3,25,26 AND GREGORY J. KEIR4,5

1Department of Respiratory Medicine, Royal Prince Alfred Hospital, Sydney, NSW, Australia; 2Central Clinical School, University of Sydney, Sydney, NSW, Australia; 3NHMRC Centre of Research Excellence in Pulmonary Fibrosis, Sydney, NSW, Australia; 4School of Medicine, University of Queensland, Brisbane, QLD, Australia; 5Department of Respiratory Medicine, Princess Alexandra Hospital, Brisbane, QLD, Australia; 6Department of Respiratory Medicine, John Hunter Hospital, Newcastle, New South Wales, Australia; 7Department of Respiratory Medicine, Alfred Health, Melbourne, VIC, Australia; 8School of Medicine, University of Adelaide Hospital, Adelaide, SA, Australia; 9Lung Research Laboratory, University of Adelaide, Adelaide, SA, Australia; 10Respiratory Services, Auckland District Health Board, Auckland, New Zealand; 11Department of Medical Imaging, The Prince Charles Hospital Brisbane, QLD, Australia; 12Department of Allergy, Immunology and Respiratory Medicine, Monash University, Melbourne, VIC, Australia; 13Department of Respiratory Medicine, The Alfred, Melbourne, VIC, Australia; 14Department of Physiotherapy, Alfred Health, Melbourne, VIC, Australia; 15Institute for Breathing and Sleep, Melbourne, VIC, Australia; 16Queensland Lung Transplant service, The Prince Charles Hospital, Brisbane, QLD, Australia; 17Central Clinical School, Monash University, Melbourne, VIC, Australia; 18Department of Rheumatology, Royal Prince Alfred Hospital, Sydney, NSW, Australia; 19Advanced Lung Disease Unit, Fiona Stanley Hospital, Perth, WA, Australia; 20Department of Medicine, University of Notre Dame Australia, Fremantle, WA, Australia; 21Physiotherapy Department, Austin Health, Melbourne, VIC, Australia; 22Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand; 23Department of Respiratory Medicine, Austin Hospital, Melbourne, VIC, Australia; 24Melbourne Medical School, University of Melbourne, Melbourne, VIC, Australia; 25University of Western Australia, Institute for Respiratory Health, Perth, WA, Australia; 26Department of Respiratory Medicine, Fiona Stanley Hospital, Perth, WA, Australia

ABSTRACT

Pulmonary complications in CTD are common and can involve the interstitium, airways, pleura and pulmonary vasculature. ILD can occur in all CTD (CTD-ILD), and may vary from limited, non-progressive lung involvement, to fulminant, life-threatening disease. Given the potential for major adverse outcomes in CTD-ILD, accurate diagnosis, assessment and careful consideration of therapeutic intervention are a priority. Limited data are available to guide management decisions in CTD-ILD. Autoimmune-mediated pulmonary inflammation is considered a key pathological pathway in these disorders, and immunosuppressive therapy is generally regarded the cornerstone for major adverse outcomes in CTD-ILD. However, the natural history of CTD-ILD in individual patients can be difficult to predict, and deciding who to treat, when and with what agent can be challenging. Establishing realistic therapeutic goals from both the patient and clinician perspective requires considerable expertise. The document aims to provide a framework for clinicians to aid in the assessment and management of ILD in the major CTD. A suggested approach to diagnosis and monitoring of CTD-ILD and, where available, evidence-based, disease-specific approaches to treatment have been provided.

Key words: clinical diagnosis and management, collagen vascular disease, connective tissue disease, interstitial lung disease.

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INTRODUCTION

The connective tissue diseases (CTD) include a variety of disease entities characterized by end-organ damage mediated by immune system overactivity. Pulmonary complications are common and can involve the interstitium, airways, pleura, pulmonary vasculature and chest wall. Interstitial lung disease (ILD) can occur in all CTD (CTD-associated ILD (CTD-ILD)), and may vary from limited, non-progressive lung involvement, to fulminant, life-threatening disease. Given the potential for major adverse outcomes in CTD-ILD, accurate diagnosis, assessment and careful consideration of therapeutic intervention are a priority.

In contrast to well-defined diagnostic criteria and evidence-based treatment recommendations for idiopathic pulmonary fibrosis (IPF), limited data are available to guide management decisions in CTD-ILD. Autoimmune-mediated pulmonary inflammation is considered a key pathobiological pathway in these disorders, with immunosuppressive therapy generally accepted as the cornerstone of treatment for severe and/or progressive CTD-ILD. However, the natural history of CTD-ILD in individual patients can be difficult to predict, and deciding who to treat, when and with what agent can be challenging. Establishing realistic therapeutic goals from both the patient and clinician perspective requires considerable expertise.

This document aims to provide a framework for clinicians to aid in the assessment and management of ILD in the major CTD. Non-ILD and extra-pulmonary manifestations of CTD will not be discussed in detail. A suggested approach to diagnosis and monitoring of CTD-ILD and, where available, evidence-based, disease-specific approaches to treatment have been provided.

Methods

This position paper highlights important aspects in the diagnosis and treatment of CTD-ILD, with particular reference to Australia and New Zealand. The document is not intended as a treatment guideline. G.J.K. was appointed as the chair of a 26-member panel with expertise in CTD-ILD, including 17 respiratory physicians, two rheumatologists and an immunologist, pathologist, radiologist, physiotherapist, exercise physiologist, respiratory nurse and patient representative.

After initial face-to-face discussion, specific sections were assigned to individual authors for comprehensive literature review. All authors had the opportunity to review all content and referenced articles, and contribute to all sections in subsequent meetings (conducted as both face-to-face and telephone discussions). Summary statements have been provided at the end of each major section. These statements are based on published data where available (with specific references cited) or expert opinion by consensus agreement where evidence is lacking. Two authors (A.S.J. and G.J.K.) compiled and edited the final manuscript that was reviewed and approved by all authors. The committee did not receive any commercial sponsorship and all panel members worked on an honorary basis.

APPROACH TO DIAGNOSING CTD-ILD

Clinical diagnosis of CTD

All CTD can be associated with ILD and, when present, accounts for substantial morbidity and mortality. The estimated prevalence of ILD in the major CTD is shown in Table 1. In most cases of CTD-ILD, the underlying CTD is established at the time of diagnosis. However, ILD can be the presenting (forme fruste) or only manifestation of an underlying CTD. For example, ILD is the presenting disease manifestation in up to 10% of rheumatoid arthritis (RA) patients, while in clinically amyopathic dermatomyositis (CADM), anti-synthetase syndrome and systemic sclerosis (SSc) sine scleroderma, ILD may persist as the only manifestation of the CTD. Therefore, in all patients with ILD it is vital to assess for subtle and non-volunteered features of CTD based on history and clinical examination.
A non-exhaustive list of the clinical signs and symptoms associated with the major CTD is presented in Table 1. In practice, a reasonable screening approach would include enquiry for the presence of inflammatory joint pain or stiffness, Raynaud’s phenomenon (especially recent onset), rashes, sicca symptoms (dry eyes and/or dry mouth) or skeletal muscle symptoms (e.g. proximal weakness and myalgia), combined with examination for synovitis, cutaneous signs (e.g. mechanic’s hands and malar rash) and proximal muscle strength. A rheumatology review may be helpful if symptoms or signs are difficult to interpret or if further investigations are being considered.

International consensus classification criteria for specific CTD are referenced (Table 1) and are a helpful guide for diagnosis. In addition, some patients have ‘overlap’ features across several diagnoses, and some patients do not fulfill criteria for specific CTD. In the context of ILD, these patients may be considered as meeting the research criteria for interstitial pneumonia with autoimmune feature (IPAF).

**Table 1** Summary of estimated prevalence, clinical signs and symptoms, manifestations and non-ILD respiratory manifestation in the major CTD

| CTD       | Prevalence of ILD                      | Clinical signs and symptoms                  | ILD manifestations | Non-ILD respiratory manifestations |
|-----------|---------------------------------------|----------------------------------------------|--------------------|-----------------------------------|
| SSc       | Detectable: up to 75% Clinically significant: 25–45% | Raynaud’s phenomenon Sclerodactyly Digital ulcers/pits Telangiectasia Skin thickening GI involvement | Most common: NSIP Other: UIP, OP | PAH Pulmonary lymphoma Aspiration pneumonia |
| RA        | Detectable: 30–60% Clinically evident: 10–30% | Polymarticular synovitis Rheumatoid skin nodules | Most common: UIP Other: NSIP, OP | Bronchiectasis, bronchiolitis Rheumatoid lung nodules Pleural disease ± effusion Respiratory muscle weakness |
| IIM       | 30–50% Up to 80% in anti-synthetase syndrome | Proximal symmetrical muscle weakness Gottron’s sign Gottron’s papules Heliotrope rash Shawl sign Mechanic’s hands | Most common: NSIP Other: OP, AIP/DAD | |
| SLE       | Detectable: up to 30% Clinically evident: 3–11% | Photosensitive and/or malar rash Oral ulcers Alopecia Serositis | Most common: NSIP Other: LIP, OP, UIP, FB, AIP/DAD | Pleuritis Diffuse alveolar haemorrhage Respiratory muscle weakness ‘Shrinking lung syndrome’ |
| SJS       | 10–30% | Sicca symptoms Enlarged parotid glands | Most common: NSIP Other: OP, LIP, UIP, FB | MALT lymphoma Amyloidosis Bronchiectasis Pleuritis Diffuse alveolar haemorrhage Respiratory muscle weakness Aspiration pneumonia |
| MCTD      | 20–85% | Swollen hands Synovitis Myositis Acrosclerosis Raynaud’s phenomenon | Most common: NSIP Other: UIP, OP | |

AIP, acute interstitial pneumonia; CTD, connective tissue disease; DAD diffuse alveolar damage; FB, follicular bronchiolitis; GI, gastrointestinal; IIM, idiopathic inflammatory myopathy; LIP, lymphocytic interstitial pneumonia; MALT, mucosa-associated lymphoid tissue; MCTD, mixed CTD; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; PAH, pulmonary arterial hypertension; RA, rheumatoid arthritis; SJS, Sjögren’s syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

**Serology**

Testing for the presence of autoantibodies is an integral step in the diagnostic work up for a suspected CTD and closely interacts with the clinical assessment summarized above. Certain autoantibody profiles are characteristic or strongly suggestive of a particular CTD, can focus clinical assessment for other organ involvement and assist with determining prognosis and treatment. The development of tests for extended autoantibody profiles, such as the myositis-specific autoantibody (MSA) panel, has helped more accurately identify and characterize patients with CTD-ILD, especially when disease manifestations are subtle. Typical radiological findings (such as rapidly progressive organizing pneumonia (OP), characteristic of anti-synthetase...
syndrome) may also prompt more detailed serological testing. Major treatment decisions can hinge upon serology, for example, in amyopathic dermatomyositis (DM) where the combination of a positive autoantibody and ILD may be the only evidence of a CTD. Autoantibodies and their disease associations are shown in Table 2 and discussed in more detail in disease-specific sections.

The most common methods for detecting autoantibodies are indirect immunofluorescence (e.g. anti-nuclear antibody (ANA) and double-stranded DNA (dsDNA) autoantibodies), enzyme-linked immunosorbent assay (ELISA; e.g. extractable nuclear antigen (ENA) screen, dsDNA autoantibodies and anti-cyclic citrullinated peptide (CCP) antibody) and line immunoblot (e.g. MSA panel). Individual centres may have access to immunoprecipitation or other bespoke immunological techniques. Each technique has unique strengths and weaknesses, balancing sensitivity, specificity, reproducibility, cost and convenience. Different laboratories employ various techniques and may modify the thresholds used to report ‘positive/negative’ or ‘borderline’ results. Thus, serology results must always be interpreted within the clinical context of each patient and not simply taken at ‘face value’. The input of a rheumatologist or immunologist on the relative importance of positive results can be helpful in the clinical context.

### Imaging

The principal roles of high-resolution computed tomography (HRCT) in the evaluation of suspected CTD-ILD are to: (i) confirm the presence of ILD and (ii) provide a radiological classification of disease pattern. Almost all radiological patterns can occur in CTD-ILD, with a non-specific interstitial pneumonia (NSIP) pattern the most frequently observed (Table 1, Fig. 1). The exception is RA where the usual interstitial pneumonia (UIP) pattern predominates and is predictive of poorer outcome. Other common radiological patterns include OP, lymphocytic interstitial pneumonia (LIP) and some patients may demonstrate a variety of overlapping HRCT patterns. Thin-section volumetric computed tomography (CT, 0.5–1.5 mm) is essential for optimal spatial resolution and appreciation of parenchymal detail. Prone sequences help establish whether abnormalities reflect true disease or gravity-dependent change, particularly relevant in the radiological diagnosis of early (or mild) NSIP. Sequences obtained during full expiration highlight features of air-trapping, relevant in the CTD associated with small airways disease (including bronchiectasis, obliterative bronchiolitis and follicular bronchiolitis). Indeed, airways disease can be an early manifestation of RA-associated ILD (RA-ILD), and inspiratory sequences may appear normal or near-normal. HRCT also aids the assessment of complications such as infection.

### Table 2 Most common auto-Ab associations in the major CTD

| CTD                                | Auto-Ab                              | Clinical associations                                      |
|-------------------------------------|--------------------------------------|------------------------------------------------------------|
| Systemic sclerosis                  | ANA, Anti-centromere, Anti-Scl 70 (topoisomerase I), Anti-RNA polymerase I, III | Strong association with PAH; ‘limited’ disease |
|                                    |                                      | Strong association with ILD; ‘diffuse’ disease            |
|                                    |                                      | Increased risk of renal crisis with concomitant corticosteroid use |
|                                    |                                      | Not included on most ENA panels                           |
| RA                                 | RF, Anti-CCP                         | Strong association with RA-ILD                             |
|                                    | Anti-CCP                             | Associated with high prevalence of ILD                    |
| Idiopathic inflammatory myositis    | Myositis-specific Ab: Anti-tRNA synthetase (Jo-1, PL7, PL12, EJ, OJ), MDA5, Mi2, TIF1y, NXP2, SAE SRP, HMGCR Myositis-associated Ab: PM-Scl, Ro52, Ku | May be associated with rapidly progressive ILD |
|                                    |                                      | TIF1y, NXP2 increased risk of malignancy                  |
|                                    |                                      | IMNM; severe muscle disease                               |
|                                    |                                      | Also detected in other CTD                                |
| Systemic lupus erythematosus        | ANA, Anti-dsDNA, Anti-Sm, -RNP, -ribosomal P Anti-Ro60 (SSA), -Ro52, -La (SSB) | Present in >95% of cases                                  |
|                                    |                                      | Titre often correlates with disease activity               |
| Sjögren’s syndrome                  | ANA, Anti-Ro60 (SSA), -Ro52, -La (SSB) | Some patients may have a positive RF                      |
| Mixed connective tissue disease     | ANA, Anti-RNPs                        |                                                           |
|                                    | Anti-RNP                             |                                                           |
drug-induced pneumonitis, acute exacerbations and malignancy, with increased incidence among certain CTD.23,27,29–32 HRCT also allows rapid evaluation of ILD extent, largely independent of confounding factors (e.g. concurrent emphysema or pulmonary hypertension (PH)) which may impact pulmonary function tests (PFT).

The syndrome of combined pulmonary fibrosis with emphysema (CPFE) has been described in RA and SSc, sometimes without a significant smoking history.33 As with idiopathic CPFE, this may represent a distinct clinical phenotype in genetically susceptible individuals with appropriate tobacco exposure. Pleuroparenchymal fibroelastosis (PPFE) is a rare entity that has recently been described in a mixed cohort of CTD patients and may be associated with increased risk of respiratory-related death.34

**Histopathology**

Similar to radiological patterns, NSIP is the predominant histopathological sub-type found in CTD-ILD (except for RA) and often overlaps with other patterns such as OP and UIP (Table 1).35–37 Even where radiology may initially demonstrate more inflammatory changes such as ground-glass opacification, CTD-ILD can evolve to a pattern more in-keeping with UIP, with ‘honeycomb’ cystic lung destruction and irreversible fibrosis. Extent of traction bronchiectasis and extent of honeycombing are independent predictors of mortality and are more likely to develop if the inflammatory ILD is left untreated or under-treated in its earlier stages.38

**Lung biopsy selection and techniques**

Lung biopsy is generally not required for the diagnosis of CTD-ILD, with HRCT highly specific for discriminating disease pattern in this population.37,39 Histopathology can have prognostic implications but this information seldom influences treatment decisions. Lung biopsy may be necessary to exclude non-autoimmune causes for pulmonary infiltrates or nodules (e.g. malignancy) and a reasonable strategy would be to discuss the need for biopsy at a multidisciplinary meeting (MDM) prior to proceeding.

In the rare situations where lung biopsy is considered in CTD-ILD, options include transbronchial lung biopsy using forceps, transbronchial lung cryobiopsy and video-assisted thoracoscopic surgery (VATS) surgical lung biopsy. For investigation of nodules, radiologic-guided core biopsy may be reasonable, but has limited utility outside of this indication. VATS lung biopsy is the gold standard for histopathological sampling of lung parenchyma and provides a diagnostic yield of over 88% in ILD.2 With an overall morbidity rate of 10–30% and mortality risk of 1–2%, this modality should be reserved for younger patients with well-preserved physiology and fewer comorbidities.40,41
general, the small biopsy size and sampling error of traditional transbronchial biopsy limit its role in the diagnosis of ILD, but may be considered in airway-centred processes such as OP. Cryobiopsy has been shown to have superior diagnostic yield compared with conventional forceps biopsy in studies of mixed ILD populations, with larger tissue sample size and absence of crush artefact. The recently published Cryobiopsy versus Open Lung Biopsy in the Diagnosis of Interstitial Lung Disease (COLDICE) study reported high levels of agreement between cryobiopsy and surgical lung biopsy for both histopathological interpretation and MDM diagnoses in patients with difficult to classify ILD who required histopathological evaluation to aid diagnosis.

Current American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society (ATS/ERS/JRS/ALAT) IPF diagnostic guidelines do not make recommendations for or against the use of cryobiopsy for ILD diagnosis outside of expert centres. A recent expert consensus statement from the American College of Chest Physicians provides guidance for the procedural aspects of cryobiopsy, without specific recommendations on cryobiopsy application in CTD-ILD.

Bronchoscopy and lavage
Bronchoscopy with bronchoalveolar lavage (BAL) may be indicated in the CTD-ILD patients with unexplained radiological lung infiltrates. Analysis of BAL cellular composition and microbial cultures can help distinguish possible differential diagnoses including infection, haemorrhage and drug-induced eosinophilic infiltrate. BAL leucocyte differential counts in CTD-ILD have been described in the research setting but seldom influence treatment decisions.

Multidisciplinary meeting
Comprehensive description of the core features, governance and constitution of the ILD-MDM have recently been detailed in a joint Thoracic Society of Australia and New Zealand (TSANZ)/Lung Foundation Australia position statement.

In brief, the ILD-MDM consists of the face-to-face discussion of clinical and diagnostic material by clinicians caring for the patient with respiratory physicians, a radiologist and, if relevant, a histopathologist with expertise in ILD (Fig. 2). Rheumatologists may also play an important role in the ILD-MDM, with CTD-ILD among the most common presentations to the ILD-MDM after IPF.

Specific studies on the role of MDM in CTD-ILD are limited. Walsh et al. investigated the agreement between seven ILD-MDM for the diagnosis of 70 ILD cases. Agreement for a diagnosis of CTD-ILD was the highest for any ILD (weighted kappa: 0.73). However, independent clinician agreement before MDM discussion was already high (weighted kappa: 0.76), suggesting that MDM discussion may not be essential if CTD-ILD diagnosis is clear cut. However, MDM also aid the re-classification of previously unrecognized CTD-ILD, mainly from unclassifiable and ‘IPF’ referrals, with important implications for prognosis and management. The frequency of CTD-ILD diagnosis increased from 10% to 21% after MDM discussion in a study of 90 consecutive ILD-MDM cases.

With the evolution of ILD nomenclature (including the Fleischner criteria), and the nuances of designating likely histology from HRCT appearances, the ILD-MDM is an increasingly important forum for integrating ‘clinical context’ with HRCT patterns, informing prediction of disease behaviour and treatment decisions. In addition, in complex CTD-ILD cases, the ILD-MDM may be useful in staging severity and assessing serial change.

SUMMARY
- Integration of clinical, serological and HRCT findings, coupled with ILD-MDM discussion, is key to confirming an accurate diagnosis of CTD-ILD.
- NSIP is the most frequent radiological and histological ILD pattern seen in association with CTD.
- Lung biopsy generally does not contribute significant additional diagnostic or prognostic information and should be reserved for cases of major diagnostic uncertainty following ILD-MDM discussion.

APPROACH TO MANAGEMENT OF CTD-ILD

General principles of monitoring and treatment
Given the heterogeneous disease course of CTD-ILD, accurate prognostication involving staging of ILD severity and assessment of disease progression is important when making treatment decisions. An understanding of the natural history of the specific CTD-ILD in question also provides important information. For example, whilst SSc-associated ILD (SSc-ILD) may follow a relatively indolent course and require only careful monitoring, myositis-associated ILD (idiopathic inflammatory myopathy-associated ILD (IIM-ILD)) can progress rapidly, necessitating intensive immunosuppressive therapy. Importantly, drug-induced ILD and infection (including opportunistic infection) should always be considered in the setting of new-onset interstitial changes in CTD, particularly in those receiving immunosuppressive therapy.

Staging and prognostication
Staging CTD-ILD severity at diagnosis allows survival estimation and establishment of a baseline from which to gauge future change. In addition to clinical examination, baseline investigations typically include PFT, HRCT and echocardiography in certain circumstances (e.g. SSc-ILD).

There is no universally accepted staging system for CTD-ILD, with several different models proposed. The ILD-GAP index (ILD subtype, gender, age and
pulmonary function tests) has been validated across a range of ILD, including CTD-ILD. An important exception appears to be IIM-ILD, where the ILD-GAP model is a poor predictor of mortality risk. In SSC-ILD, an algorithm based on HRCT appearances and PFT defines ‘limited’ or ‘extensive’ disease (Fig. 3). Both staging systems demonstrate similar survival estimates for patients with more severe or extensive CTD-ILD, identifying a population that may benefit from treatment intervention. Disease trajectory is a powerful prognostic determinant and longitudinal measurement of PFT is vital to monitoring ILD progression. A decline in forced vital capacity (FVC) ≥10% and/or diffusing capacity for carbon monoxide (DLCO) ≥15% on serial measures indicates clinically significant disease progression and is associated with increased mortality risk. However, even ‘marginal’ declines (e.g. <10% FVC) can represent progressive ILD in the appropriate context, particularly if associated with deterioration in symptoms and other measures (e.g. oxygen saturation and 6-min walk distance). A number of unique confounders should be kept in mind when interpreting PFT in CTD-ILD, including concomitant PH contributing to a reduced DLCO, and the presence of muscular weakness, pleural disease and/or thoracic skin thickening (particularly in diffuse cutaneous SSc) that can reduce lung volumes independent of the ILD.

HRCT provides important diagnostic and staging information, but serial HRCT is not recommended to routinely monitor disease progression. Repeat HRCT imaging may be useful to corroborate a decline in PFT

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**Figure 2** Suggested algorithm for the diagnosis and management of connective tissue disease-associated interstitial lung disease (CTD-ILD). For detailed discussion, see the section ‘Deciding when to treat’.
and exclude other causes of deterioration (e.g. infection, pulmonary embolism and malignancy). Computer-based quantitative CT analysis and molecular and genetic biomarkers as objective measures of disease prognosis are exciting and evolving research areas, not yet validated for clinical use.\textsuperscript{60,61}

**Deciding when to treat**

Accurately distinguishing patients with inherently stable CTD-ILD who can be carefully observed without treatment, from those at risk of progression requiring therapy is one of the most challenging aspects of CTD-ILD management.\textsuperscript{62,63} Whilst the goal of treatment in most cases of CTD-ILD is to achieve stability and prevent further progression, a number of important exceptions to this rule exist and are discussed in more detail below. The decision to treat and the intensity of treatment are influenced by a variety of factors including the CTD subtype, ILD severity, observed disease trajectory and mitigating patient factors. Progressive ILD, particularly in the context of recent onset systemic CTD manifestations, is another important factor influencing treatment decisions. The presence of extra-pulmonary CTD manifestations (e.g. active synovitis in RA for which mycophenolate and azathioprine are largely ineffective) may also impact treatment strategies, highlighting the importance of multidisciplinary involvement between respiratory physicians, rheumatologists and immunologists. Referral to an ILD expert centre may be useful when deciding who, when and how to treat. Treatment approaches based on estimated disease behaviour, coupled with treatment goals and monitoring strategies, have been adapted from the idiopathic interstitial pneumonias (IIP) and summarized in Table 3.

Treatment strategies are largely drawn from studies in SSc-ILD and extrapolated to the other CTD-ILD. Whilst reasonable in the absence of specific evidence, caution is required, especially in more progressive CTD-ILD, such as IIM-ILD. CTD-ILD that is limited (HRCT extent <20\% and/or FVC >70\%) with stable lung

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### Table 3 Disease behaviour, treatment goals and intervention in CTD-ILD

| Disease behaviour | Treatment goal | Intervention and monitoring |
|------------------|---------------|-----------------------------|
| Reversible, self-limited | Achieve regression | Short-term (3–6 months) observation to confirm disease regression |
| Reversible, with risk of progression | Achieve regression and then stabilize | Intensive/higher dose treatment with short-term monitoring to ensure response. Then, rationalize to maintenance treatment and long-term observation to ensure stability |
| Stable, risk of progression | Maintain status | Maintenance treatment. Monitor for disease progression |
| Progressive, irreversible with potential for stabilization | Stabilize | Intensive/higher dose treatment and then rationalize to maintenance treatment. Short-term monitoring to ensure response and then long-term observation to ensure stability |
| Progressive, despite treatment | Slow disease progression | Rescue therapy Trials Transplantation Palliative/best supportive case |

Adapted from Travis et al.,\textsuperscript{64} with permission.

CTD-ILD, connective tissue disease-associated interstitial lung disease.

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\(\text{HR}=3.46; \text{p}<0.0005\)

Figure 3 (A) A simple staging system for systemic sclerosis-associated interstitial lung disease (SSc-ILD). (B) Survival curves for SSc-ILD patients with ‘limited’ versus ‘extensive’ disease (hazard ratio (HR) = 3.46; \(\text{p}<0.0005\)) (Adapted from Goh et al.,\textsuperscript{54} with permission).
## Table 4  Common immunosuppressive therapies utilized in CTD-ILD

| Medication and mechanism | Dosage | Adverse effects | Screening and monitoring |
|--------------------------|--------|-----------------|-------------------------|
| **Corticosteroids**      |        |                 |                         |
| Bind to the intracellular glucocorticoid receptor → inhibits cytokine transcription → | Start 0.5 mg/kg/day. Aim to taper down to 10–20 mg maintenance | Diabetes | BP |
| (1) ↓ T cells (IL2 inhibited) | | Weight gain | Serum glucose |
| (2) Eosinophil apoptosis (directly or by inhibition of IL5) | | Hypertension | Lipid profile |
| (3) Macrophage inhibition (blocking IL1 and TNF-α) | | Myopathy | Eye examination |
| (4) Leucocytosis | | Osteoporosis | Bone densitometry |
| B cells are not significantly inhibited | | Accelerated atherosclerosis | |
| **AZA** | 2.0–2.5 mg/kg/day if TPMT within normal limits | Bone marrow suppression | TPMT |
| Inhibits DNA and RNA synthesis in mainly T cells but also B cells | | GI intolerance | FBC and LFT |
| **MMF and enteric-coated mycophenolate sodium** | MMF: start 500 mg bd, titrating to 2–3 g daily (in two divided doses) | Bone marrow suppression | FBC, LFT, renal function |
| Inhibits DNA synthesis in T and B cells | MMF 500 mg = enteric-coated mycophenolate sodium 360 mg | Hepatotoxicity | |
| **Cyclophosphamide** | 600 mg/m², maximum dose 1000 mg | Toxicity to bladder and gonads | Maintain adequate fluid intake to avoid bladder toxicity |
| Alkylating agent toxic to all human cells to differing degrees with haematopoietic cells forming a sensitive target | Monthly for maximum 6 months | • <250–300 mg/kg cumulative dose to avoid gonadal toxicity | Monthly urinalysis |
| **Tacrolimus** | Start 1 mg bd titrating by 1–2 mg daily with at least 7 days between adjustments. Aim for 12 h trough level 5–8 ng/mL | Increased vascular constriction → ↓ BP, ↓ renal perfusion | Trough levels 10–14 days after initiating and at regular intervals |
| Prevents calcineurin-dependent gene transcription in T cells | | Contraindicated in pregnancy (category D) | Monitor BP, BGL, FBC, EUC, LFT, lipids |
| **Rituximab** | Initiation: two 1 g infusions, 2 weeks apart | Hepatitis B reactivation | Screen for hepatitis B (surface antigen and core antibody) |
| B-cell depletion by targeting CD20 lasting 6–9 months | Maintenance: 1 g every 6–12 months | Should not be taken in pregnancy (category C) | |
| **Methotrexate** | Start 5–15 mg/week, escalating by 5 mg/month to maximum 25–30 mg/week | Hypogammaglobulinaemia | FBC, LFT, EUC |
| Inhibits dihydrofolate reductase | | Pulmonary toxicity | |
| | | Hepatotoxicity | |
| | | Bone marrow suppression | |
| | | Alopecia | |

Continued
function over time can generally be closely monitored with serial PFT and clinical assessment (Fig. 3A). In contrast, extensive and/or progressive ILD usually warrants treatment.\(^5\) However, extensive ILD alone is not an indication for therapy with established fibrosis with stable lung function and symptoms less likely to respond to immunosuppression and careful monitoring without pharmacotherapy may be appropriate. A suggested algorithm for the broad management of CTD-ILD is shown in Figure 2.

Pharmacological/immunosuppressive treatment

Immunosuppression is the mainstay of pharmacotherapy in CTD-ILD, aiming to reduce inflammation, minimize progression to established fibrosis and permanent loss of lung function.\(^6\) The general mechanism of action is to interfere with critical pathways in the inflammatory cascade including B- and T-cell function, and inhibit pro-inflammatory cytokines, although precise mechanisms are poorly understood.\(^6\) The major classes of immunosuppressive medications, their mechanism of action and potential adverse effects are summarized in Table 4. Prior to commencement of immunosuppressive therapy, screening for active/latent microorganisms and organ dysfunction is recommended due to the increased risk of new or reactivated infection (e.g. tuberculosis (TB) and hepatitis) and side effects.\(^6\)

The intensity of immunosuppressive therapy is tailored to the individual CTD, acuity of ILD presentation, therapeutic expectations and patient factors. For example, rapidly progressive ILD as seen in IIM and systemic lupus erythematosus (SLE) often presents with a radiological pattern of OP or diffuse alveolar damage (DAD), suggesting a predominantly inflammatory process. In such situations, intensive immunosuppression with pulse intravenous (IV) methylprednisolone, IV cyclophosphamide or rituximab may be required with the expectation of achieving reversal of inflammation and minimizing permanent lung damage.\(^6\)\(^,\)\(^6\) In contrast, SSc-ILD may be more slowly progressive and lower dose maintenance therapy to achieve stabilization rather than major improvement is a realistic therapeutic goal. Specific treatment approaches are discussed in more detail in relevant disease sections and currently available evidence from treatment trials is summarized in Table 5.

Anti-fibrotic therapy has recently been found to be of benefit in CTD-ILD. Annual rate of decline in FVC was lower in patients with SSc-ILD and progressive fibrosing-ILD who received nintedanib compared with placebo in the Safety and Efficacy of Nintedanib in Systemic Sclerosis (SENSCIS) and Nintedanib in Progressive Fibrosing Lung Disease (INBUILD) trials, respectively.\(^8\)\(^,\)\(^6\) INBUILD included a range of fibrosing ILD, incorporating 170 patients with 'autoimmune' ILD, including RA-ILD, SSc-ILD and mixed CTD (MCTD)-associated ILD (MCTD-ILD). Although not powered to provide evidence for a benefit of nintedanib in specific diagnostic subgroups, results suggest that nintedanib reduces the rate of ILD progression (measured by FVC decline) in patients with chronic, progressive fibrosing ILD.\(^6\) Pirfenidone has also shown potential benefit in patients with progressive unclassifiable ILD, including a subgroup with IPAF. Slower disease progression was observed in study participants receiving pirfenidone compared with placebo over 24 weeks.\(^8\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^8\)\(^,\)\(^8\) While encouraging, neither nintedanib nor pirfenidone has regulatory approval for the treatment of CTD-ILD in Australia or New Zealand at this time and the exact role of these agents (including patient selection, timing and combination with immunosuppressive therapy) for CTD-ILD remains to be determined.

Special considerations

Identification of patients at risk of infectious complications is prudent prior to commencement of immunosuppressive therapy. Screening for latent TB infection (LTBI) and hepatitis B is the most well recognized, while hepatitis C, human immunodeficiency virus (HIV) and strongyloides infection should be considered on an individual patient basis.

Latent TB infection

The lifetime risk of reactivation in LTBI is approximately 5–10% and increases with immunosuppressive therapy. The risk of TB reactivation increases by up to 25-fold, highest in the first 12 weeks, after commencement of tumour necrosis factor (TNF) inhibitors (e.g. infliximab and adalimumab). Thus, LTBI screening with an interferon-gamma release assay (IGRA) or Mantoux tuberculin skin test (TST) is recommended in all patients where TNF inhibitors are being considered.\(^9\) Patients with LTBI should be treated prior to commencement of TNF inhibitor therapy, which reduces the incidence of TB reactivation by more than 80%.\(^6\)\(^,\)\(^8\)\(^,\)\(^8\) LTBI screening/treatment for other immunosuppressive medications is less clear. Studies have reported a seven-fold increased risk of TB reactivation in patients on corticosteroids.\(^8\)\(^,\)\(^,\)\(^9\) Evidence to recommend LTBI treatment for all patients is currently insufficient, but it is reasonable to evaluate overall risk (steroid dose,
| Study | Study design | Intervention | Outcome |
|-------|-------------|--------------|---------|
| Systemic sclerosis | **Scleroderma Lung Study I**<sup>68</sup> | Prospective RCT  
$n = 158$  
Duration: 12 months | Oral CYC (up to 2 mg/kg daily) vs placebo  
Mean absolute improvement in FVC at 12 months of 2.53%, favouring CYC, greater frequency of AE in the CYC arm | |
| | **FAST study**<sup>69</sup> | Prospective RCT  
$n = 45$  
Duration: 12 months | IV CYC (600 mg/m<sup>2</sup>, monthly for six doses) + low-dose prednisolone (30 mg alternate days) followed by AZA (2.5 mg/kg/day; max 200 mg) vs placebo  
Trend to improvement FVC (4.19%; $P = 0.08$) in the active treatment arm, although statistically non-significant | |
| | **BUILD 2 (Bosentan)**<sup>70</sup> | Prospective RCT  
$n = 163$  
Duration: 12 months | Bosentan 125 mg bd vs placebo  
No increase in SAE in the active treatment group | |
| | **Scleroderma Lung Study II**<sup>71</sup> | Prospective RCT  
$n = 142$  
Duration: 24 months | MMF 1.5 g bd vs oral CYC (up to 2.0 mg/kg/day) for 12 months followed by placebo for 12 months  
Significant improvement in FVC from baseline in both arms (2.2% and 2.9%: MMF vs CYC), with no difference in FVC change between the groups | |
| | **LOTUSS (pirfenidone)**<sup>72</sup> | Randomized, open label  
$n = 63$  
Duration: 16 weeks | Comparison of two pirfenidone up-titration regimens: 2-week titration vs 4-week titration, to a maintenance dose of 801 mg tds  
Greater frequency of AE in the CYC group  
‘Acceptable’ tolerability profile, although a longer up-titration may be associated with better tolerability | |
| | **Pomalidomide (CC-4047)**<sup>73</sup> | Prospective RCT  
$n = 23$  
Duration: 12 months | Pomalidomide 1 mg/day vs placebo  
Negative co-primary end points with no difference in FVC, mRSS or GI symptoms at 52 weeks  
Enrolment discontinued early due to difficult recruitment | |
| | **faSScinate**<sup>74</sup> | Prospective RCT  
$n = 87$  
Duration: 48 weeks | Tocilizumab 162 mg subcutaneous weekly vs placebo  
Negative secondary end point with no change in FVC or DL<sub>CO</sub> from baseline to 48 weeks | |
| | **SENCIS (nintedanib)**<sup>75</sup> | Prospective RCT  
$n = 576$  
Duration: 12 months | Nintedanib 150 mg bd vs placebo  
Positive primary end point with reduced annual rate of change in FVC in subjects receiving nintedanib compared to placebo (~52.4 mL vs ~93.3 mL per year; $P = 0.04$) | |
| | **Rituximab**<sup>76</sup> | Open-label, comparative study  
$n = 51$  
Duration: 4 years (range: 1–7 years)  
Rituximab ($n = 33$) vs conventional immunosuppression (MMF, AZA or MTX) ($n = 18$)  
At 2 years, improvement in FVC compared to baseline in rituximab group, with no change in FVC in conventional immunosuppression group | | |
| | **SCOT study**<sup>77</sup> | Randomized, open-label  
$n = 75$  
Duration: 54 months | Myeloablative stem cell transplantation ($n = 36$) vs IV CYC ($n = 39$)  
Positive composite primary end point (incorporating death, event-free survival, FVC) | |
| Study                     | Study design                      | Intervention                                                                 | Outcome                                                                 |
|--------------------------|-----------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| **ASTIS study**<sup>78</sup> | Randomized, open-label            | Autologous stem cell transplantation <sup>n</sup> = 79 vs IV CYC <sup>n</sup> = 77 | Positive primary end point (death or persistent major organ failure) favouring stem cell transplantation |
|                          | <sup>n</sup> = 156               |                                                                              | Increased stem cell treatment-associated mortality in the first 12 months |
|                          | Duration: 5.8 years              |                                                                              | Positive primary end point (improvement in mRSS or FVC) favouring stem cell transplantation |
| **ASSIST study**<sup>79</sup> | Randomized, open-label            | Non-myeloablative stem cell transplantation <sup>n</sup> = 10 vs IV CYC <sup>n</sup> = 9 | Positive primary end point (improvement in mRSS or FVC) favouring stem cell transplantation |
|                          | <sup>n</sup> = 19                |                                                                              |                                                                          |
|                          | Duration: 12 months              |                                                                              |                                                                          |
| **RA**                   | Retrospective review              | All had RA with UIP. Forty-one percent received glucocorticoids ± immunosuppression due to poor baseline lung function or progressive RA with UIP | Fifty percent of treated group improved or had stable lung function |
| **Song et al.**<sup>80</sup> | <sup>n</sup> = 84               | MMF (1–1.5 g bd)                                                            | Trend to improvement in FVC following MMF commencement, with reduction in prednisolone requirement |
|                          | Median f/u: 33 months            |                                                                              |                                                                          |
| **IIM**                  | Retrospective review              | Rapidly progressive IIM-ILD <sup>n</sup> = 10: IV CYC IIM-ILD but less rapidly progressive <sup>n</sup> = 10 | Stabilization in IIM-ILD following IV CYC |
| **Schnabel et al.**<sup>82</sup> | Prospective open label          | Rapidly progressive IIM-ILD <sup>n</sup> = 10: IV CYC (10–30 mg/kg every 3–4 weeks), prednisolone >0.5 mg/kg/day and cyclosporine A (2–4 mg/kg/day) | Fifty percent mortality rate at 3 months |
|                          | <sup>n</sup> = 20                |                                                                              |                                                                          |
|                          | Median f/u: 35 months            |                                                                              |                                                                          |
| **Kameda et al.**<sup>83</sup> | Prospective open label          | Rapidly progressive IIM-ILD <sup>n</sup> = 10: IV CYC (10–30 mg/kg every 3–4 weeks), prednisolone >0.5 mg/kg/day and cyclosporine A (2–4 mg/kg/day) | Fifty percent mortality rate at 3 months |
|                          | <sup>n</sup> = 27                |                                                                              |                                                                          |
| **Huapaya JA et al.**<sup>148</sup> | Retrospective review          | AZA <sup>n</sup> = 66                                                        | Improved FVC% and DL<sub>CO</sub>% predicted in AZA group |
|                          | <sup>n</sup> = 110               | MMF <sup>n</sup> = 44                                                         | Improved FVC% predicted in MMF group |
|                          | f/u: 24–60 months               |                                                                              | Lower prednisolone dose in both groups |
|                          |                                       |                                                                              | More frequent AE in AZA group |

6MWD, 6-min walk distance; AE, adverse event; ASSIST, American Scleroderma Stem Cell versus Immune Suppression Trial; ASTIS, Autologous Stem cell transplantation; AZA, azathioprine; bd, twice daily; CTD-ILD, connective tissue disease-associated ILD; CYC, cyclophosphamide; DL<sub>CO</sub>, diffusing capacity for carbon monoxide; f/u, follow-up; FVC, forced vital capacity; GI, gastrointestinal; IIM, idiopathic inflammatory myopathy; IIM-ILD, IIM-associated ILD; ILD, interstitial lung disease; IV, intravenous; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; MTX, methotrexate; n, number; RA, rheumatoid arthritis; RCT, randomized controlled trial; SAE, serious AE; SCOT, Scleroderma: Cyclophosphamide or Transplantation trial; SENSICS, Safety and Efficacy of Nintedanib in Systemic Sclerosis; tds, three times daily; UIP, usual interstitial pneumonia.
concomitant immunosuppressive medications, exposures and background incidence), and consider LTBI testing and treatment on an individual basis.

**Hepatitis B**

Hepatitis B virus (HBV) reactivation associated with immunosuppressive therapy is associated with significant morbidity and mortality. The American Gastroenterological Association guidelines on the prevention and treatment of HBV reactivation during immunosuppressive drug therapy stratify patients into high-, moderate- or low-risk groups based on the serological pattern (e.g. HBV surface antigen positivity) and immunosuppressive agent. Expert hepatology opinion is strongly recommended if active or previous HBV is detected.

**Pneumocystis jirovecii**

*Pneumocystis jirovecii* pneumonia (PJP) is a potentially life-threatening infection, most prevalent in patients receiving high-dose glucocorticoids combined with other immunosuppressive agents. There are published guidelines for the use of PJP prophylaxis in HIV, cancer and solid organ transplant recipients. No guidelines exist for CTD patients on immunosuppression, but is an important consideration given the generally long-term nature of immunosuppressive therapy in CTD. It is reasonable to recommend prophylaxis (e.g. sulfamethoxazole and trimethoprim) in patients receiving sustained daily corticosteroids of 20 mg/day or greater. Prophylaxis in the context of other immunosuppressants is less clear but should be considered in patients on combinations of immunosuppressants despite lower doses of prednisolone.

**SUMMARY**

- Treatment decisions in CTD-ILD are influenced by CTD diagnosis and duration since diagnosis, ILD severity, disease trajectory, extra-pulmonary CTD manifestations and individual patient factors.
- Progressive CTD-ILD with a predominant inflammatory component (determined following clinical and radiological evaluation) may be amenable to significant reversal with appropriate intensive immunosuppression.
- Progressive and/or severe CTD-ILD with a predominant fibrotic component typically do not regress significantly with intensive immunosuppression, although stabilization may be achieved with low-dose corticosteroids, with or without a steroid-sparing immunosuppressive agent. New data support the potential role for anti-fibrotic therapy in such cases, although this is not yet approved for use in Australia or New Zealand.
- Serial PFT is the cornerstone of CTD-ILD monitoring, including response to treatment.
- Evaluation for latent infection (e.g. TB and hepatitis) and appropriate opportunistic infection prophylaxis should be considered on an individual patient basis prior to initiation of immunosuppressive therapy.

**SPECIFIC CTD-ILD**

**Systemic sclerosis**

SSc (also known as scleroderma) is characterized by autoimmunity, fibrosis of the skin and internal organs, and vasculopathy. Pulmonary complications, including ILD and pulmonary arterial hypertension (PAH), are the leading causes of morbidity and mortality in SSc. Whilst ILD may occur in up to 80% of SSc patients, only 25–30% have progressive disease and the key challenge is identifying patients at risk of disease progression and likely to benefit from treatment, whilst avoiding unnecessary drug toxicities in indolent disease.

Risk factors for developing severe, progressive SSC-ILD include: (i) SSc disease duration of less than 3 years; (ii) diffuse cutaneous SSc; (iii) presence of anti Scl-70/DNA topoisomerase 1 autoantibodies; (iv) severe gastro-oesophageal reflux disease (GORD); (v) extensive ILD; and (vi) declining lung function. Extent of ILD severity, traditionally quantified by FVC and DLCO, is the most important factor, especially in the early stages of disease. The risk of developing ILD is greatest in the first few years after SSc symptom onset, but patients can still progress after this ‘at-risk’ period. Vigilance for disease progression must always be maintained, with declining lung function associated with increased mortality.

A simple staging system, incorporating semi-quantitative assessment of disease extent on HRCT and FVC, classifies patients into limited and extensive disease (Fig. 3A). Patients who have <20% or ≥20% disease on HRCT are classified as limited or extensive disease, respectively. If HRCT extent is ‘indeterminate’, an FVC threshold of above or below 70% predicted is used to distinguish limited versus extensive disease, respectively. This approach has been validated in other SSC-ILD cohorts and provides greater prognostic insight than either HRCT extent or FVC measures alone.

The goal of treatment in most cases of severe and/or progressive SSC-ILD is to achieve disease stabilization, rather than major reversal. The use of corticosteroids remains debatable, but when used, dosage should be minimized (<10–15 mg/day), to reduce the risk of side effects and SSc renal crisis. The *Scleroderma Lung Study I* (SLS I) demonstrated modest improvements in lung function, dyspnoea and health-related quality of life (HRQoL) with cyclophosphamide, administered as either a monthly infusion or daily oral dose for 12 months. Although the latest European League Against Rheumatism (EULAR) recommendations advocate for the use of cyclophosphamide in SSc-ILD, this is now outdated. Instead, mycophenolate mofetil (MMF) has increasingly been the first drug of choice following the findings from the *Scleroderma Lung Study II* (SLS II). Whilst the beneficial effect on lung function was similar between oral MMF and oral cyclophosphamide given over 24 months, MMF was associated with better tolerability and less adverse effects. However, in patients with rapidly progressive disease, IV cyclophosphamide is still considered the first drug of choice with a quicker onset of action.
compared to MMF. In these cases, IV cyclophosphamide could be given monthly for 6 months as the ‘induction phase’ of treatment, followed by MMF in the ‘consolidation phase’ of treatment.

The exact duration of ongoing maintenance therapy remains unclear. In the SLS I study, the benefits of cyclophosphamide were lost 12 months after the cessation of treatment. Long-term follow-up of SLS I and SLS II patients (median follow-up of 8 years) demonstrated no difference in survival between cyclophosphamide or MMF, and patients on placebo. It is likely that more than 2 years of immunosuppression is required to sustain improvements in lung function and symptoms with longer term studies required. An observational study of 30 SSc-ILD patients receiving 24 months of IV cyclophosphamide followed by ongoing low-dose immunosuppression (azathioprine, methotrexate (MTX) or MMF) demonstrated sustained improvement in lung function in the ensuing 5 years and no significant adverse events.

The SENSCIS trial demonstrated a reduced decline in FVC in SSc-ILD patients on nintedanib compared with placebo (–52.4 vs. –93.3 mL/year, respectively, P = 0.04), but does not support nintedanib as a substitution for immunotherapy in SSc-ILD. The magnitude of benefit depended on MMF use, suggesting the potential benefit of MMF on lung function. Furthermore, there were no benefits reported with HRQoL measures or modified Rodman skin score (mRSS) and nintedanib should not be considered a disease-modifying agent for SSc. It remains unclear if nintedanib should be used following or together with immunosuppressive therapy. The U.S. Food and Drug Administration recently approved nintedanib for the treatment of SSc-ILD, but is not yet approved for this indication in Australia or New Zealand.

Several additional therapeutic options including pirfenidone, tocilizumab and rituximab are currently being evaluated for SSc-ILD. Tocilizumab, an anti-IL6 monoclonal antibody, has recently been investigated in a phase III study of SSc patients, including 31% with ILD (NCT02453256). Preliminary analysis demonstrated preservation of FVC over 48 weeks, less decline in FVC compared with placebo and improvements of fibrosis as assessed by HRCT with final analysis awaited.

Stem cell transplantation for SSc-ILD
There are no stem trials in SSc-ILD per se, but secondary lung function end points in broader SSc studies are interesting. Two randomized trials of non-myeloablative autologous haematopoietic stem cell transplant (HSCT)—the American Scleroderma Stem Cell versus Immune Suppression Trial (ASSIST) and Autologous Stem cell transplantation (ASTIS) trial—reported less SSc disease progression with HSCT compared with cyclophosphamide. ASTIS also demonstrated superior event-free survival, overall survival and improvement in FVC and total lung capacity (TLC) over a median follow-up time of 5.8 years. The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial compared myeloablative autologous HSCT to cyclophosphamide in severe SSc, including 73 (97%) participants with pulmonary involvement. HSCT was superior to cyclophosphamide in terms of Global Rank Composite Score (comprising in hierarchical order: death, event-free survival, FVC, Health Assessment Questionnaire-Disability Index (HAQ-DI) and mRSS) and change in FVC. Notably, patients with severe lung disease (FVC <45% or DLCO <40% predicted) were excluded, as were those with left ventricular ejection fraction <50%, severe renal impairment, PAH or more than 6 months of previous treatment with cyclophosphamide.

SUMMARY
- Risk factors for severe and/or progressive SSc-ILD include greater extent of ILD on HRCT, declining PFT, Scl-70 autoantibody positivity and development of ILD early in the SSc disease course.
- MMF has been demonstrated to stabilize SSc-ILD and is generally regarded as the initial therapy of choice when treatment is required. Azathioprine or cyclophosphamide (typically IV, given the lower cumulative toxicity) may be an alternative to MMF.
- The use of concomitant corticosteroids is controversial and if prescribed, the dose should be minimized (<10–15 mg/day) to reduce side effects including the risk of SSc renal crisis.
- Nintedanib has been shown to slow lung function decline in SSc-ILD, although it is not yet approved for this indication in Australia or New Zealand.
- HSCT may improve SSc-ILD and survival in highly selected SSc patients, although its role is likely to be limited to specialist centres.

Rheumatoid arthritis
Interstitial changes on HRCT occur in up to 40–50% of newly diagnosed RA patients, with up to 10% developing clinically significant ILD during their lifetime. ILD may precede articular symptoms or appear many years after RA diagnosis. Male gender, older age at RA onset, smoking history, positive rheumatoid factor (RF) and anti-CCP antibodies are associated with increased risk of ILD. Both RA-ILD and IPF share a number of genetic risk factors, including the MUC5B promoter variant, and genes associated with telomere maintenance (TERT, TERC and TINF2). Given the high prevalence of subclinical ILD in RA, a low threshold for respiratory investigation in patients with seropositive RA is suggested. ILD has been reported in patients with anti-CCP antibodies without a clinical diagnosis of RA, but it is unknown what proportion progress and develop clinically apparent joint disease.

Ufip is the most common radiological and histopathological pattern in RA, followed by NSIP, OP and, rarely, acute interstitial pneumonia (AIP) or LIP. RA-Ufip is associated with poorer survival, with most but not all studies suggesting a prognosis similar to IPF. Other negative prognostic factors include lower baseline PFT and declining PFT in the first 6 months.
There are no randomized controlled trials (RCT) assessing immunosuppressive therapy specifically in RA-ILD. Case series and retrospective series report stabilization or improvements in lung function with corticosteroids, conventional immunosuppressive agents (e.g. cyclophosphamide, azathioprine and MMF) and rituximab. RA-ILD with UIP may be less responsive to immunosuppressive therapy, although retrospective series have reported stabilization of pulmonary function with MMF. Given the increased morbidity and mortality associated with immunosuppression in IPF, the decision to immunosuppress in RA-ILD requires caution. The recently reported INBUILD study demonstrated reduced rate of decline in FVC in a mixed cohort of patients with progressive fibrosing ILD, including 89 patients with RA-ILD. As of July 2020, a multicentre trial of pirfenidone in RA-ILD (NCT02800871) is ongoing.

In patients with established RA-ILD, the safety of MTX and other potentially pneumotoxic disease-modifying antirheumatic drugs remains under debate. While MTX pneumonitis is a recognized rare adverse event (estimated prevalence of 0.43% in RA patients), the impact of MTX on established RA-ILD remains uncertain. MTX treatment was not associated with an increased risk of RA-ILD in a cohort of 2701 patients with newly diagnosed RA. Furthermore, a case series of 78 patients with RA-ILD (two-thirds receiving MTX) reported improved survival in the MTX subgroup. Thus, pre-existing ILD is not a specific contraindication to MTX therapy, but caution is advised in patients with limited respiratory reserve.

Leflunomide and other biologic agents (e.g. TNF inhibitors, rituximab and tocilizumab) have all been associated with pulmonary toxicity, but it is unknown if pre-existing ILD is an independent risk factor. Given these uncertainties, caution and vigilance for a decline in lung function is required if considering these agents in patients with RA-ILD.

**SUMMARY**

- In RA-ILD, a UIP pattern, lower baseline PFT and declining PFT are associated with a poorer prognosis.
- Controlled treatment trial data for managing RA-ILD are lacking. A variety of immunosuppressive agents (including cyclophosphamide, azathioprine, MMF or rituximab) may be effective in ameliorating decline in RA-ILD.
- In the setting of progressive RA-ILD, consideration should be given to cessation of disease-modifying anti-therapeutic drugs (leflunomide and TNF inhibitors), given the potential for these agents to precipitate worsening ILD.
- Clinical trials evaluating nintedanib and pirfenidone for RA-ILD are ongoing.

**Idiopathic inflammatory myopathy**

The IIM spectrum of disorders includes polymyositis (PM), DM, inclusion body myositis (IBM) and immune-mediated necrotizing myopathy (IMNM). ILD is a major cause of morbidity and mortality in PM/DM, with an estimated prevalence of 20–65%, including rapidly progressive ILD. IBM and IMNM are not typically associated with pulmonary involvement and will not be discussed.

The recently revised IIM diagnostic criteria incorporate demographic, clinical, serological and muscle biopsy features to determine the likelihood of disease (Table 1). Pragmatically, myositis in the presence of cutaneous features (including mechanic’s hands, Gottron’s papules and a heliotrope rash) supports a diagnosis of DM, while positive muscle biopsy findings and elevated serum creatinine kinase (CK) in the absence of cutaneous features suggests PM. CADM is a subgroup of IIM with cutaneous findings in the absence of myositis.

Autoantibodies are a key diagnostic feature in IIM and are broadly classified into MSA and myositis-associated autoantibodies (MAA) (Table 2). In most pathology laboratories in Australia and New Zealand, these antibodies are not included in standard ENA testing, and need to be specifically requested. Of the MSA, the presence of anti-tRNA synthetase antibody (most commonly anti-Jo1) is a defining feature of the anti-synthetase syndrome and highly associated with ILD (prevalence up to 71%). While the anti-MDA5 antibody may be associated with CADM and rapidly progressive ILD (particularly in individuals of Asian ethnicity), it may also be associated with a more benign clinical course. Specific IIM phenotypes are associated with an increased risk of malignancy, especially lung, breast, colorectal and pancreas and targeted screening may be appropriate. Positive anti-TIF1γ and anti-nuclear matrix protein (NXP)-2 antibodies in particular have a reported 27- and 3.68-fold higher risk of malignancy, respectively, among DM patients.

Subclinical ILD appears to be less common in IIM compared with other CTD, with the majority of IIM-ILD patients tending to have more severe, progressive lung involvement requiring treatment. In the absence of randomized controlled data, several treatment recommendations have been proposed by expert groups. Oral prednisolone (0.25–1 mg/kg) for 3–8 weeks followed by slow wean has been reported to result in clinical improvement in 90–100% of patients. Treatment of rapidly progressive IIM-ILD includes pulse IV methylprednisolone or IV cyclophosphamide, followed by steroid-sparing oral agents. Azathioprine, MMF, calcineurin inhibitors (cyclosporine and tacrolimus) and rituximab have all demonstrated benefit in case series with small patient numbers. A recent retrospective study of 110 IIM-ILD patients treated with azathioprine (n = 66) or MMF reported similar improvements in PFT and reduced prednisolone requirements, although a higher frequency of adverse events were observed in the azathioprine group. IV immunoglobulin (IVIG) is beneficial in active muscle disease, although efficacy for ILD specifically remains unclear. Plasmapheresis is generally reserved for severe multiorgan disease, although evidence for its role specifically in IIM-ILD is limited. Due to the risk of worsening or relapsed
ILD, immunosuppression is generally maintained for a relatively long duration (often >2–5 years), although controlled treatment data are lacking. Despite treatment, morbidity and mortality related to IIM-ILD are significant, with 25% of patients deteriorating despite treatment and an overall ILD-associated mortality rate of 13.5% at 5 years in one case series.146

**SUMMARY**

- ILD is a major contributor to IIM mortality and warrants expedited evaluation and treatment.137,138
- Initial intensive immunosuppression with high-dose corticosteroids (oral or IV), IV cyclophosphamide or rituximab is often required to achieve control in progressive IIM-ILD. IVIG and plasmapheresis may play a role in the acute setting.145,147,151,152,154
- Maintenance immunosuppression with low-dose corticosteroids and steroid-sparing agents (including MMF, azathioprine and calcineurin inhibitors) is generally required following initial high-dose therapy, without evidence of an obviously superior agent.146–149

**Other CTD**

**Systemic lupus erythematosus**

Clinically significant pulmonary complications involving the interstitium, pulmonary vasculature and/or pleura occur in 3–8% of SLE patients.155 ILD is uncommon, but in rare cases, heralded by life-threatening acute lupus pneumonitis and diffuse alveolar haemorrhage. Whilst elevated erythrocyte sedimentation rate (ESR) and/or hypocomplementaemia are indicators of systemic SLE disease activity, the presence of autoantibodies (e.g. ANA and anti-dsDNA) do not correlate with the risk of ILD.156–158

Pleural disease is the most common pulmonary manifestation, with pleurisy and/or pleural effusion occurring in over 60% of patients.159 Shrinking lung syndrome is a rare, poorly understood complication of SLE, characterized by pleuritic chest pain, restrictive physiology and no interstitial changes on imaging.5 Other pulmonary manifestations of SLE include PH and thromboembolic disease, especially in association with antiphospholipid syndrome.160,161

**Sjögren’s syndrome**

Clinically significant ILD is rare in Sjögren’s syndrome (SjS), and most commonly follows a mild, self-limited disease course.155,162 SjS-associated ILD (SjS-ILD) is typically more female predominant, with a median age of onset of 60 years and occurring 5–10 years after SjS diagnosis.134 Autoantibodies do not predict risk of SjS-ILD, although presence of anti-Ro/SS-A autoantibodies correlated with a lower DLCO in one case series.163 LIP was previously considered the most common radiological pattern in SjS, but recent reports suggest NSIP predominates.36 It is important to distinguish dry mucous membranes (xerotracea) as a cause or contributor to symptoms, especially dry cough, independent of ILD.155

SjS patients are at increased risk for lymphoma, especially mucosa-associated lymphoid tissue (MALT) lymphoma.155,164 Pulmonary lymphoma occurs in 1–2% of patients with primary SjS, and accounts for approximately 20% of all SjS-associated lymphoma.165 It is important to distinguish pulmonary lymphoma from LIP. Both can manifest with ground-glass opacification, cysts, parenchymal nodules and lymphadenopathy.158 Other rare pulmonary complications in SjS include pleuritis, vascular disease (PAH and pulmonary embolism), amyloidosis, ‘shrinking lung’ and ‘middle lobe’ syndromes.158,166–169

**Undifferentiated and mixed connective tissue disease**

Undifferentiated CTD (UCTD) is a term used to describe the early, ‘undifferentiated’ phase of a CTD with clinical symptoms and signs of a CTD and non-specific laboratory abnormalities (e.g. ANA and ENA), not satisfying diagnostic criteria for a defined CTD. UCTD does not have a well-accepted definition and is broadly encompassed within the IPAF definition (discussed later).170 Approximately one-third of UCTD patients progress to a definable CTD over 5-year follow-up.171 MCTD has a distinct clinical phenotype and human leucocyte antigen (HLA) profile, although controversy remains with four available diagnostic criteria.17,172,173

The central concept of MCTD is an overlap syndrome associated with anti-U1 ribonucleoprotein (anti-RNP) antibodies.174 Peak incidence is around the age of 40 years.174 Clinical features always include Raynaud’s phenomenon and at least two of: myositis, arthritis, oesophageal dysmotility, leucopaenia, serositis and ILD or PAH.174 Diagnosis is challenging due to the overlap of clinical features with other CTD and requires continual reassessment.

HRCT abnormalities occur in approximately half of MCTD patients, with one-third demonstrating ILD.175 Anti-Ro52 antibodies are a potential marker of lung involvement.175 MCTD-ILD is severe in approximately one-fifth of patients, and associated with a 21% mortality compared with 3% in patients with a normal HRCT.175

**Treatment of SLE, SjS, UCTD and MCTD-ILD**

The optimal therapy for ILD associated with SLE, SS, UCTD and MCTD is unknown due to a lack of controlled treatment trials. In clinical practice, broad CTD-ILD treatment principles remain pertinent with therapeutic intervention based on ILD severity and rate of progression, other organ involvement and comorbidities. Extrapolating from treatment trials in other CTD, mild, non-progressive ILD may be monitored, whilst treatment with immunosuppression (e.g. corticosteroids, azathioprine and MMF) is reasonable where there is evidence of progression. Treatment trials on the utility of rituximab in these CTD are ongoing.176
SUMMARY

- ILD is a recognized complication in SLE, SJ S, UCTD and MCTD but is typically less frequent than the other CTD.
- Limited data exist to guide treatment decisions in this group with therapeutic approaches generally extrapolated from other CTD.
- In severe and/or progressive ILD, high-dose corticosteroids in combination with a steroid-sparing agent (MMF or azathioprine) is a reasonable initial treatment approach.
- Several unique pulmonary complications may occur in SJ S (lymphoma and amyloidosis) and SLE (lupus pneumonitis and pulmonary haemorrhage), requiring a high degree of diagnostic suspicion to enable timely diagnosis.

Interstitial pneumonia with autoimmune features

While ILD can develop in the context of a known CTD, it is increasingly recognized that some patients with idiopathic ILD have features of autoimmune disease, but do not fulfil criteria for a defined CTD. Historically, various terms including ‘UCTD-associated ILD’, ‘lung-dominant CTD’ or ‘autoimmune-featured ILD’ have been used to describe such patients, impeding uniform study of this important cohort. In 2015, a ERS/ATS Taskforce defined this group as ‘IPAF’. The proposed classification criteria remain a research framework rather than clinical classification, requiring revision and validation in future studies.

The full criteria consist of three domains—clinical, serological and morphological (Table 6). Qualifying individuals must demonstrate characteristics from at least two of the three domains. Serological evaluation includes a broad array of autoantibodies including an extended ENA and myositis panel, high titre ANA and RF level. Multi-compartment involvement in the morphological domain includes ILD with unexplained pleuro-pericardial involvement, pulmonary vasculopathy or airways disease.

Since publication of the IPAF classification criteria, several retrospective single-centre studies have described IPAF populations with heterogeneous demographics, clinical features and natural history. One landmark study demonstrated no difference in survival between IPAF and IPF patients, although there was a clear demarcation in survival between those with and without a UIP pattern on HRCT. However, other studies have not replicated this finding and larger multicentre, prospective studies are needed.

Little is known about the best clinical approach to managing patients who meet the IPAF research criteria. Indeed, IPAF is likely to be comprised of a heterogeneous group of patients, in which different therapies are targeted at different patient phenotypes. At present, a pragmatic approach would be to consider the underlying ILD diagnosis by ILD-MDM and treat the patient accordingly. In patients who are considered to have...
CTD-ILD, treatment will usually follow an approach similar to SSc-ILD, whereas, in patients considered to have IPF, anti-fibrotic therapy may be appropriate. The recently published pirfenidone in unclassifiable ILD study included 33 (13%) patients with IPAF, too small a number to make meaningful conclusions. Ongoing studies in this patient population are required.

**SUMMARY**

- IPAF identifies a heterogeneous patient group with ILD and features suggestive of a CTD, not meeting established classification criteria for a specific CTD.
- It remains a research framework rather than clinical diagnosis.
- There is no current consensus for the management of patients meeting IPAF criteria, with several ongoing studies evaluating the role of immunosuppressive and antifibrotic therapies.

**Vasculitis and ILD**

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), incorporating granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA) may affect the lung parenchyma, blood vessels and airways. While diffuse alveolar haemorrhage and parenchymal mass lesions (with or without cavitation) are the most frequent pulmonary manifestations of AAV, ILD is an increasingly recognized complication, particularly in MPA where there is an estimated prevalence of 7-36% and significant associated morbidity.

Positive ANCA serology has been reported in 4-10% of patients with a confirmed diagnosis of IPF. However, the significance of myeloperoxidase (MPO) or proteinase 3 (PR3) antibodies remains uncertain, with inconsistent clinical and radiological findings reported in several small single-centre studies.

Recently, a large retrospective cohort of 745 IPF patients from two North American expert ILD centres identified ANCA in 34 (4.6%) patients at the time of IPF diagnosis. Of the ANCA-positive patients, 18 (53%) were MPO-antibody positive, 10 PR3-antibody positive (29%) and 6 (18%) with non-specific ANCA positivity. ANCA positivity was not associated with baseline IPF severity or transplant-free survival. During follow-up (median: 18 months), 28% of MPO-positive patients developed clinically significant vasculitis, most commonly renal disease and mononeuritis multiplex. No PR3-positive or non-specific ANCA patients developed clinical vasculitis.

Treatment for systemic vasculitis usually involves guideline-recommended immunosuppressive regimens, but data specific to AAV-associated ILD (AAV-ILD) are limited. Some case series suggest clinical or radiological improvement with immunosuppressive therapy, but impact on overall survival and progression of lung disease remains controversial and further research is required. Generally speaking, ILD occurring in the context of positive ANCA serology without clinical evidence of vasculitis should be treated on its merits, based on the principles discussed in section ‘Approach to management of CTD-ILD’.191,192

**SUMMARY**

- The association between AAV and ILD, particularly IPF, is increasingly recognized, although variable clinical manifestations have been reported in published series.
- Positive MPO serology appears to be more strongly linked to the development of systemic vasculitis.
- Optimal treatment, including the use of immunosuppressive therapy, remains the focus of ongoing research.

**Psoriasis and ILD**

There are small retrospective case reports and case series of ILD in patients with psoriasis and psoriatic arthritis, although a clear pathogenic association is yet to be determined. Observed radiological patterns on HRCT include UIP, NSIP and OP with descriptions of non-specific bilateral lower zone predominant ground-glass opacities with irregular reticular changes. Most reported cases are mild with minimal or no respiratory symptoms. Correlation between dermatological and pulmonary disease activity, and response of pulmonary disease to immunosuppressive treatment for the skin, is also variable. Small case numbers limit meaningful conclusions and further prospective studies are required to determine if a clear association with ILD exists, and to clarify prevalence and pathogenic mechanisms. Careful observation for pulmonary complications in patients with psoriasis, as with any systemic inflammatory disease, is reasonable.

**SPECIAL CONSIDERATIONS IN CTD-ILD MANAGEMENT**

**CTD-ILD with pulmonary hypertension**

PH is defined as a mean pulmonary artery pressure of ≥25 mm Hg at rest on right heart catheterization (RHC), although a revised threshold of ≥20 mm Hg in combination with a pulmonary vascular resistance of ≥3 Wood Units has recently been proposed. Clinical conditions associated with PH are classified into five groups based on similar pathophysiological mechanisms, characteristics and management, as outlined in the updated World Health Organization (WHO) World Symposium on Pulmonary Hypertension classification. In CTD-ILD, it is important to ascertain whether PH is a primary vasculopathy (i.e. PAH ‘CTD-PAH’; WHO Group 1 PAH) or secondary to the underlying CTD-associated ILD (‘CTD-ILD-PH’; WHO Group 3 PH). Furthermore, PH secondary to left heart disease (WHO Group 2 PH) may also be present, further complicating classification of these patients. The presence of PH regardless of cause is a poor prognostic marker. The ASPIRE Registry estimated a 5-year survival of 25%...
for SSc-associated PAH and 30% for PH secondary to lung disease. A recent study demonstrated similarly for SSc-associated PAH and 30% for PH secondary to DI.

Diagnosis and management of CTD-ILD may require careful evaluation at an experienced PH centre. Ancillary investigations suggesting Group 3 PH require careful evaluation at an experienced PH centre. Group 3 PH in CTD-ILD patients is often complex and requires major clinical trials evaluating PAH-specific therapies permitted mild impairments in lung function.

In Group 1 PAH, pulmonary vasodilator therapies have proven therapeutic benefit. SSc is the dominant CTD associated with PAH (estimated prevalence of 8–12%), but PAH can also occur in RA, SLE and MCTD. PAH-specific therapies include endothelin receptor antagonists, phosphodiesterase (PDE5) inhibitors, the cyclic GMP stimulator riociguat and prostacyclin analogues. The European Society of Cardiology (ESC)/ERS guidelines advocate a 'treat to target' approach using combination PAH–drug therapy, with commencement of therapy in those with WHO Functional Class II symptoms. Current regulatory restrictions in Australia and New Zealand only fund one agent at a time for patients with WHO Functional Class IIa symptoms.

Conversely, PAH-specific therapies are generally not beneficial in Group 3 PH, with potential for worsening ventilation/perfusion (V/Q) mismatch and consequent hypoxaemia. Management should focus on treating the ILD and hypoxaemia. Evidence-based guidelines for the management of PH coexisting with moderate- to severe CTD-ILD do not currently exist.

General management of all CTD patients with PH includes diuresis, supervised exercised programmes and domiciliary oxygen as required. As for all PH, there is no clear evidence for anticoagulation (in the absence of another indication), pregnancy should be avoided and anaesthesia carries significant additional risks.

### SUMMARY
- Elevated pulmonary pressure in the setting of CTD carries a significant negative prognostic impact and warrants evaluation at an experienced PH centre.
- In CTD-PAH (WHO Group 1), pulmonary vasodilator therapies are beneficial and should be instituted once a PAH diagnosis is confirmed, ideally at WHO functional class II level.
- Treatment escalation of CTD-PAH with combination therapy as per the ESC/ERS guidelines is recommended.
- PH complicating CTD-ILD (WHO Group 3) should prompt optimization of ILD therapy and correction of hypoxaemia.

### Lung transplantation for CTD
Approximately 9–12% of CTD-ILD patients progress to end-stage respiratory failure, despite appropriate immunosuppressive therapy and lung transplantation are potential treatment options. CTD is not a relative or absolute contraindication to transplantation, yet less than 2% of all lung transplants worldwide between 1995 and 2010 were for patients with CTD-associated lung disease. Factors complicating transplant management and outcomes in CTD include immune dysregulation, GORD, renal disease and active myositis. Oesophageal dysfunction is common in CTD patients, especially in those with SSc, and GORD is potentially associated with the development of chronic lung allograft dysfunction and post-transplant morbidity and mortality. The presence of untreated significant dysfunction of another major organ system (e.g. heart, liver, kidney or brain) is an absolute contraindication unless combined organ transplantation can be performed.

Recent studies suggest that carefully selected CTD patients with pulmonary disease warrant transplantation assessment, with similar post-transplant outcomes to other cohorts. Evaluation of 284 lung transplantations in CTD patients from 1991 to 2009 included in the United States Organ Procurement and Transplantation Network database reported that there were no post-transplant recurrences of CTD lung disease, extrapulmonary flares of the CTD were rare (one possible flare per 20.3 patient years) and cumulative survival was similar to IPF patients.

This was echoed by a single-centre cohort study of 892 lung transplant recipients, including 72 with SSc-ILD and 311 with pulmonary fibrosis from other causes (other ILD). SSc-ILD recipients demonstrated satisfactory short-term survival (100% 30-day and 80.6% 1-year survival) and no difference in 5-year survival (conditional on 1-year survival) compared to other ILD (66% vs 58%, respectively, P = 0.249). Importantly, SSc-ILD recipients also had superior bronchiolitis obliterans syndrome (BOS)-free survival. Careful evaluation with 24 h pH monitoring and oesophageal manometry (before and/or early after transplant) may aid reflux management, including planning laparoscopic fundoplication post-transplant as a strategy for long-term allograft protection.

Case series of successful transplant outcomes are emerging for myositis patients, but the presence of active myositis requiring immunosuppression pre-transplant, especially steroids, may complicate post-transplant management, rehabilitation and outcomes.
SUMMARY

- In selected CTD-ILD patients, survival following lung transplantation is comparable to non-CTD patients with similar restrictive lung disease.²¹⁵
- Given the unique challenges in CTD-ILD, early assessment by an experienced transplant physician should be undertaken in those patients with severe and/or progressive lung disease who may be suitable transplant recipients.

Non-pharmacological management in CTD-ILD

People with CTD-ILD often experience dyspnoea, fatigue, anxiety, depression, cough and reduced exercise tolerance.¹⁵⁵,²¹⁸ These symptoms are debilitating and substantially affect HRQoL.²¹⁹,²²⁰ The CTD are further complicated by other systemic manifestations including arthropathy, vasculopathy, exercise-induced hypoxaemia and corticosteroid-induced myopathies which may further impair exercise tolerance. Non-pharmacological strategies such as pulmonary rehabilitation (PR), supplemental oxygen and the early integration of palliative care can positively impact symptoms and HRQoL in this population.

Pulmonary rehabilitation

There is increasing evidence that PR is effective at improving exercise tolerance, dyspnoea and HRQoL in ILD.²²¹–²²³ Whilst there are no RCT of PR in CTD-ILD specifically, one study including patients with CTD-ILD found clinically meaningful benefits in HRQoL in subgroup analysis, despite limited improvements in exercise capacity. PR is strongly recommended in the British Thoracic Society PR guidelines for all patients functionally limited by dyspnoea.²²²,²²⁴ It is possible that musculoskeletal limitations (joint pain, swelling and stiffness) may limit the gains in exercise capacity that can be achieved with traditional PR. Alternative strategies could include water-based training, which is effective in COPD patients with physical comorbidities.²²⁵ PR also incorporates education, nutrition counselling and psychological support, which may assist to improve emotional and physical well-being in this population.²²⁶,²²⁷

Supplemental oxygen

Clinical practice guidelines provide strong recommendations for the use of long-term oxygen therapy (LTOT ≥18 h per day) for people with ILD who have resting hypoxaemia.²²⁸,²²⁹ This is based on studies in COPD where it is known to improve survival. Supplemental oxygen may provide symptomatic relief in patient with advanced ILD.²³⁰,²³¹ The role of oxygen therapy in people with ILD who have exertional desaturation without resting hypoxaemia is less clear. Two small studies in IPF found that oxygen significantly increased endurance time and reduced exertional dyspnoea during constant load cycling.²³²,²³³ This supports the ATS/ERS PR guidelines recommendation for supplemental oxygen during exercise training in patients who desaturate on exertion.²³⁶ A recent crossover trial of short-term (2 weeks) use of ambulatory oxygen in fibrotic ILD demonstrated a significant improvement in HRQoL.²³⁴ Longer term outcomes remain unclear. There are two current RCT including a comparison of the effects of ambulatory oxygen with room air over 3 months (NCT02286063 and NCT02551068) and the benefits of oxygen during an 8-week exercise programme (NCT02551068).

Symptom management and palliative care

Palliative care aims to alleviate symptom burden, especially dyspnoea and cough, address advance care planning and optimize HRQoL throughout the disease course.²³¹,²³⁵ Palliative care should occur in parallel with all other treatments and not be delayed until the disease is advanced.²³¹,²³⁶ As discussed, supplemental oxygen and PR play an important role in self-management and reducing dyspnoea.²²¹ Opioids, up to a dose of 30 mg morphine daily, might safely relieve dyspnoea.²³¹,²³⁰,²³¹,²³⁷,²³⁸ Evidence for the use of benzodiazepines is limited, but may be an alternative in those with dyspnoea associated with anxiety or not controlled by opioids.²³¹,²³⁵,²³⁸,²³⁹ Caution is required with both opioids and low-dose benzodiazepines associated with increased hospital admissions and mortality in patients with oxygen-dependent ILD.²⁴⁰ Treatment of cough is difficult and requires investigation for, and treatment of, GORD given its high prevalence in CTD-ILD.²³⁶,²⁴¹ Thalidomide has been shown to reduce cough in IPF, although there is no evidence of its effect in CTD-ILD.²³¹,²⁴² Gabapentin appears effective for refractory chronic cough and mucolytic agents may be useful in assisting with sputum clearance, but CTD-ILD specific data are lacking.²³²,²⁴³ Low-dose opiates may be considered to palliate cough when alternative treatments have been unsuccessful.²³⁶,²⁴¹,²⁴⁴ Non-pharmacological interventions such as hand-held fans, rollator devices, breathing exercises and speech pathology may also prove beneficial in relieving symptoms.²³¹,²³⁸,²⁴⁴,²⁴⁵ Symptom management should also address depression, anxiety, fatigue and deconditioning, for which PR and psychotherapy may be of assistance.²²⁷,²³¹,²³⁸,²⁴⁶–²⁴⁹ Education, support and assistance for self-management for both patients and caregivers is important in optimizing quality of life and in advanced care planning. Timely patient-centred end-of-life care should be offered to all patients where progressive disease is evident or expected.²³¹

SUMMARY

- In CTD-ILD, PR can help improve exercise tolerance, dyspnoea and HRQoL.
- LTOT should be offered in those patients with resting hypoxaemia. Supplemental oxygen during exercise training in those with exertional desaturation may facilitate PR outcomes.²²¹,²²⁹,²³³,²³⁴,²³⁶
FUTURE DIRECTIONS

The next 5 years will see the most significant changes in the available therapies and the evidence base supporting treatment choice for CTD-ILD. Some of the most important treatment trials in CTD-ILD are listed in Table 5. Anti-fibrotics additional to immunosuppression are an active area of current research. As discussed, the SENSCIS study demonstrated efficacy of nintedanib in SSC-ILD, and long-term safety is being evaluated in an open-label extension study (NCT03313180). The utility of pirfenidone in combination with MMF for SSc-ILD is being assessed in the Scleroderma Lung Study III (NCT03221257) and the TRAIL1 study is evaluating pirfenidone in RA-ILD (NCT02808871).

Rituximab is generally reserved for severe CTD-ILD progressing despite conventional therapy. However, rituximab as ‘induction’ therapy (1 g at baseline and 2 weeks) is being evaluated in two ongoing clinical trials—one comparing rituximab with placebo and background MMF therapy in both arms in a broad range of CTD-ILD (NCT02990286), and a second comparing rituximab with IV cyclophosphamide (600 mg/m² 4 weekly for six doses) in SSC-ILD, IIM and MCTD (NCT01862926). As discussed, tocilizumab was recently found to be associated with stabilization of FVC in SSc with final analysis awaited.

Genetic studies in CTD-ILD are only just being reported, but it seems likely that there will be increasing recognition of gene–environment interactions and their impact on disease pathogenesis and prognosis, similar to IPF and chronic hypersensitivity pneumonitis. The incorporation of genomic markers to aid in diagnosis, risk stratification and clinical decision-making together with the identification of other molecular biomarkers may be of particular importance in CTD-ILD, given the characteristically variable disease course.

The rarity of CTD-ILD in general will continue to present difficulties obtaining evidence and reimbursement for therapeutic agents, especially for orphan CTD-ILD (e.g. SJS-ILD and anti-synthetase syndrome). However, advances in diagnostic and therapeutic modalities, and the evidence base that underpins their place in clinical practice, will significantly improve both the safety and efficacy of care for all patients with CTD-ILD.

SUMMARY AND CONCLUSIONS

Management of CTD-ILD is a challenging endeavour, requiring a multidisciplinary approach in order to achieve the best possible outcomes for patients and their caregivers. Accurate diagnosis, staging of severity and monitoring progression of CTD-ILD require the at times complicated integration of clinical, radiological, physiological and serologic data, often with substantial input from non-respiratory specialists. While immunosuppression remains the mainstay of treatment for severe and/or progressive CTD-ILD, deciding when to start therapy, which agent to use and duration of therapy is a nuanced decision impacted by many clinical and patient specific factors. An ever-expanding array of treatment options, including monoclonal antibodies targeting specific molecular pathways and the antifibrotic agents, are being evaluated with promising early results and are providing new insights into disease pathophysiology.

In this position statement, we have endeavoured to provide both an overview of general principles of CTD-ILD monitoring and treatment in addition to disease-specific guidance. However, it is important to note that given the heterogeneous clinical course of many CTD-ILD, no single management strategy will capture every clinical scenario, and continued assessment and calibration of treatment approach is vital. Given the rarity of some of the CTD-ILD and absence of specific treatment evidence, by necessity therapeutic approaches are often extrapolated from other CTD-ILD with assumed similar disease mechanisms. This paucity of treatment evidence represents a major unmet clinical need across many CTD-ILD, and should remain a priority for future research. Finally, non-pharmacological therapies are a key and often overlooked aspect in the holistic care of patients with these multi-system disorders.

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Abbreviations: AAV, ANCA-associated vasculitis; Ab, antibody; AE, adverse event; AIP, acute interstitial pneumonia; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; ASSIST, American Scleroderma Stem Cell Versus Immune Suppression Trial; ASTIS, autologous stem cell transplantation; ATS, American Thoracic Society; AZA, azathioprine; BAL, bronchoalveolar lavage; BP, blood pressure; CADM, clinically amyopathic DM; CCP, cyclic citrullinated peptide; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; CTX, cyclophosphamide; DDD, daily defined dose; DM, dermatomyositis; DMD, dermatomyositis-like disease; DSS, dermatomyositis-sarcoid overlap syndrome; Early Access Program; EAP; FVC, forced vital capacity; GMP, good manufacturing practice; Hg, hemoglobin; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ITU, intensive therapy unit; JIA, juvenile idiopathic arthritis; JIM, juvenile idiopathic multisystem disease; MCTD, mixed connective tissue disease; N.E., New England; N.S., New South Wales; N.S.L.G., New South Wales Lung Group; N.S.W., New South Wales; N.Z., New Zealand; OAA, open access; ORAL, observational; PAH, pulmonary arterial hypertension; PAUIP, pulmonary arterial upregulation in interstitial pneumonitis; RAS, renal vasculitis; RCT, randomized controlled trial; RCTI, randomized clinical trial; RCTO, randomized clinical trial observer; Ref, reference; RHEUM, Rheumatology; RJM, Roman Jakobson; Sars, severe acute respiratory syndrome; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis interstitial lung disease; SSC, systemic sclerosis; TJC, T.J. Connolly; TNSC, trianosylceramide; VAD, vascular access device; VAP, ventilator associated pneumonia; VCE, ventilator cuffed endotracheal; VD, ventilator dependent; VESI, ventilator endotracheal suctioning.
REFERENCES

1 Wells A, Denton CP. Pulmonary complications of connective tissue disease. *Semin. Respir. Crit. Care Med.* 2019; 40: 45–6.

2 Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Benoist S, Lederer DJ, Behr J, Cottin V, Danoff SK, Morel F et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/ERS/ALAT clinical practice guideline. *Am. J. Respir. Crit. Care Med.* 2018; 198: e44–68.

3 Jo HE, Troy LK, Keir G, Chambers DC, Holland A, Goh N, Wilsher M, de Boer S, Moodley Y, Grainge C et al. Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: a position statement from the Thoracic Society of Australia and New Zealand. *Respirology* 2017; 22: 1436–58.

4 Suzuki A, Kondo H, Fischer A. Recent advances in connective tissue disease related interstitial lung disease. *Expert Rev. Respir. Med.* 2017; 11: 591–603.

5 Mira-Avendano I, Abril A, Burger CD, Dellaripa PB, Fischer A, Gotway MB, Lee AS, Lee JS, Matteson EL, Yi ES et al. Interstitial lung disease and other pulmonary manifestations in connective tissue diseases. *Mayo Clin. Proc.* 2019; 94: 309–25.

6 van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA JR, Carreira PE et al. 2013 Classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Ann. Rheum. Dis.* 2013; 72: 1747–55.

7 Ha Y, Lee Y, Kang E. Lung involvements in rheumatic diseases: update on the epidemiology, pathogenesis, clinical features, and treatment. *Biomed. Res. Int.* 2018; 2018: 6930297.

8 Wallace B, Vummidi D, Khanna D. Management of connective tissue diseases associated interstitial lung disease: a review of the published literature. *Curr. Opin. Rheumatol.* 2016; 28: 236–45.

9 Aletaha D, Neogi T, Silman AI, Funovits J, Felson DT, Biringer C, Bingham CO, Birurnen WS, Burmester GR, Bykerk VP, Cohen MD et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis Rheum.* 2010; 62: 2569–81.

10 Doyle TJ, Patel AS, Hatahu H, Nishino M, Wu G, Osorio JC, Golzarri MF, TrashosHEROS A, Chu SG, Frits ML et al. Detection of rheumatoid arthritis-interstitial lung disease is enhanced by serum biomarkers. *Am. J. Respir. Crit. Care Med.* 2015; 191: 1403–12.

11 Lundberg JE, Tjarnlund A, Bottai M, Werth VP, Pilkington C, Visser M, Alfredsson L, Amato AA, Barohn RJ, Liang MH et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Ann. Rheum. Dis.* 2017; 76: 1955–64.

12 Fathi M, Vignjevic J, Bojsen M, Tylen U, Jornfeld L, Tomling G, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis: longitudinal evaluation by pulmonary function and radiology. *Arthritis Rheum.* 2008; 59: 677–85.

13 Connon GR, Christopher-Stine L, Odds CV, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? *Chest* 2010; 138: 1464–74.

14 Aringer M, Costenbader K, Daik D, Brinks R, Mosca M, Ramsey-Goldman R, Smolen JS, Wofsy D, Boumpas DT, Kamen DL et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann. Rheum. Dis.* 2019; 78: 1151–9.

15 Roca F, Dominique S, Schmidt J, Smail A, Duba S, Levesque H, Marie J. Idiopathic lung disease in primary Sjögren’s syndrome. *Autoimmun. Rev.* 2017; 16: 48–54.

16 Shiboski CH, Shiboski SC, Seror R, Criswell LA, D’Agati V, Lieman TM, Rasmussen A, Scofield H, Vitali C, Bowman SJ et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for systemic lupus erythematosus. *Ann. Rheum. Dis.* 2016; 75: 1988–2005.

17 Swaminathan S, Chaturvedi G, O’Dwyer J, Medsger TA Jr, Talarico R, Chandra K, Arnett FC et al. Diagnostic performance of the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus: a large multicentre UK study. *Ann. Rheum. Dis.* 2018; 77: 929–37.

18 Lee JY, Lee JS, Kim JI, Park I, Park J, Seo G, Park JS et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2018; 77: 1311–17.

19 Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K, Kato T et al. Utility of the 2017 European League Against Rheumatism classification criteria for systemic lupus erythematosus in Japan: a prospective, multicentre, observational study. *J. Rheumatol.* 2019; 46: 1117–26.

20 Miyasaka N, Ueki H, Shimizu N, Ishiguro H, Morita S, Otsuka M, Fujishiro H et al. Comparison of the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus with the 2012 criteria: a prospective study. *J. Rheumatol.* 2020; 47: 513–20.

21 Miyagawa N, Sawada N, Umezawa K, Tsukada T, Yabe Y, Inagaki M, Sakai T et al. The 2019 European League Against Rheumatism criteria for systemic lupus erythematosus: a prospective, multicentre, observational study. *J. Rheumatol.* 2020; 47: 1195–202.

22 Iba Y, Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2019; 78: 811–20.

23 Iba Y, Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2019; 78: 811–20.

24 Iba Y, Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2019; 78: 811–20.

25 Iba Y, Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2019; 78: 811–20.

26 Iba Y, Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2019; 78: 811–20.

27 Iba Y, Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2019; 78: 811–20.

28 Iba Y, Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2019; 78: 811–20.

29 Iba Y, Hasegawa T, Kamiyama S, Tada M, Hori K, Akahane T, Mita K et al. Interstitial lung disease in patients with dermatomyositis and polymyositis with autoimmunity: a single-center study. *Ann. Rheum. Dis.* 2019; 78: 811–20.
Diagnosis and management of CTD-ILD

Respirology

32 Ruano CA, Lucas RN, Leal CI, Lourenco J, Pinheiro S, Bryson T, Sundaram B, Khanna D, Kazerooni EA. Connective tissue diseases.

27 Aparicio IJ, Lee JS. Connective tissue disease-associated interstitial lung disease. Semin. Respir. Crit. Care Med. 2016; 37: 468–76.

24 Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, Frankel SK, Hobbs SB, Huie TJ, Ketzer J et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Chest 2006; 130: 976–81.

23 Nair A, Walsh SL, Desai SR. Imaging of pulmonary involvement in rheumatic disease. Rheum. Dis. Clin. North Am. 2015; 41: 167–96.

22 Fischer A, Meehan RT, Feghali-Bostwick CA, West SG, Brown KK. Connective tissue disease-related interstitial lung disease. Am. J. Respir. Crit. Care Med. 2001; 164: 193–6.

21 Lenz RJ, Argento AC, Colby TV, Rickman OB, Maldonado F. Transbronchial cryobiopsies for diffuse parenchymal lung disease: a state-of-the-art review of procedural techniques, current evidence, and future challenges. J. Thorac. Dis. 2017; 9: 2106–203.

20 Troy LK, Grange R, Corte TJ, Williamson JP, Vallely MP, Cooper WA, Mahar A, Myers JJ, Lai S, Mfyadi E et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. Lancet Respir. Med. 2020; 8: 171–181.

19 Maldonado F, Danoff SK, Wells AU, Colby TV, Ryu JH, Liberman M, Wahidi MM, Frazer L, Hetzel J, Rickman OB et al. Transbronchial cryobiopsy for the diagnosis of interstitial lung disease: CHEST guideline and expert panel report. Chest 2020; 157: 1030–42.

18 Goh NSL, Veeraraghavan S, Desai SR, Cramer D, Hansell DM, Denison CP, Black CM, Du Bois RM, Wells AU. Bronchosclerotic lavage cellular profiles in patients with systemic sclerosis-associated interstitial lung disease are not predictive of disease progression. Arthritis Rheum. 2007; 56: 2005–12.

17 Prasad JD, Mahar A, Blease J, Ellis SJ, Chambers DC, Lake F, Hopkins PMA, Corte TJ, Allan H, Gaspole IN. The interstitial lung disease multidisciplinary meeting: a position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia. Respirology 2017; 22: 1459–72.

16 Jo HE, Corte TJ, Moodley Y, Levin K, Westall G, Hopkins P, Chambers D, Gaspole I. Evaluating the interstitial lung disease multidisciplinary meeting: a survey of expert centres. BMC Pulm. Med. 2016; 16: 22.

15 Walsh SL, Wells AU, Desai SR, Poletti V, Picciucchi S, Dubini A, Nunes H, Valeyre D, Brillet PY, Kambouchner M et al. Multi-centre evaluation of multidisciplinary team meeting agreement on diagnosis in diffuse parenchymal lung disease: a case-cohort study. Lancet Respir. Med. 2016; 4: 557–65.

14 Jo HE, Gaspole IN, Levin KC, McCormack SR, Mahar AM, Cooper WA, Cameron R, Ellis SJ, Cotee AM, Webster SE et al. Clinical impact of the interstitial lung disease multidisciplinary service. Respirology 2016; 21: 1348–44.

13 Lynch DA. Lung disease related to collagen vascular disease. J. Thorac. Imaging 2009; 24: 299–309.

12 Tsuchiya Y, Takayanagi N, Sugihara H, Miyahara Y, Tokunaga D, Franquet T. High-resolution CT of lung disease related to collagen vascular disease. Clin. Radiol. 2018; 73: 833.e1–e10.

11 Lynch DA. Lung disease related to collagen vascular disease. Radiol. Clin. North Am. 2001; 39: 1171–87.

10 Ruano CA, Lucas RN, Leal CI, Lourenco J, Pinheiro S, Fernandes O, Figueiredo L. Thoracic manifestations of connective tissue diseases. Curr. Probl. Diagn. Radiol. 2015; 44: 47–59.

9 Cottin V, Reix P, Khouatia C, Thivolet-Beuj F, Feldmann D, Cordier JF. Combined pulmonary fibrosis and emphysema syndrome associated with familial SFTPc mutation. Thorax 2011; 66: 918–9.

8 Enomoto Y, Nakamura Y, Colby TV, Jokoh T, Sumikawa H, Nishimoto K, Yoshimura K, Matsushima S, Oyama Y, Hozumi H et al. Radiologic pleuroparenchymal fibroelastosis-like lesion in connective tissue disease-related interstitial lung disease. PLoS One. 2017; 12: e0180283.

7 Nakamura Y, Chida K, Suda T, Hayakawa H, Iwata M, Imokawa S, Tsuchiya T, Ida M, Gemma H, Yasuda K et al. Non-specific interstitial pneumonia in collagen vascular diseases: comparison of the clinical characteristics and prognostic significance with usual interstitial pneumonia. Sarcoidosis Vasc. Diffuse Lung Dis. 2003; 20: 235–41.

6 Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest 2009; 136: 439–405.

5 Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, Kitaichi M. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest 2005; 127: 2019–27.

4 Walsh SL, Sverzellati N, Devaraj A, Keir GJ, Wells AU, Hansell DM. Connective tissue disease-related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants. Thorax 2014; 69: 216–22.

3 Parambil JG, Myers JJ, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjogren syndrome. Chest 2006; 130: 1498–95.

2 Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. Inhospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. Am. J. Respir. Crit. Care Med. 2016; 193: 1161–7.

1 Hunninghake GW, Zimmerman MB, Schwartz DA, King TE Jr, Lynch J, Hegele R, Waldron J, Colby T, Muller N, Lynch D et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am. J. Respir. Crit. Care Med. 2001; 164: 193–6.
56 Goh NS, Hoyle RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, Nicholson AG, Wells AU. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol.* 2017; 69: 1670–8.

57 ATS/ERS. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am. J. Respir. Crit. Care Med.* 2002; 165: 277–304.

58 Moore OA, Proudman SM, Goh N, Corte TJ, Rouse H, Hennessy O, Morrisroe K, Thakkar V, Saharj, Roddy J et al. Quantifying change in pulmonary function as a prognostic marker in systemic sclerosis-related interstitial lung disease. *Clin. Exp. Rheumatol.* 2015; 33(4 Suppl. 91): S111–6.

59 Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D. glucocorticoid use, other associated factors, and the risk of tuberculosis. *J. Rheumatol.* 2010; 37: 2101–7.

60 Jacob J, Bartholmai BJ, Rajagopalan S, Brun AL, Egashira R, Karwoski R, Kokosi M, Wells AU, Hansell DM. Evaluation of computer-based computer tomography stratification against outcome models in connective tissue disease-related interstitial lung disease. *Clin. Exp. Rheumatol.* 2014; 32: 1766–72.

61 Lee J, Koo Y, Park C, Lee S, Lee J, Koo Y, Park C, Lee S, Lee J. Immunohistochemical analysis of Prifedine in patients with scleroderma-associated interstitial lung disease: the LOTUS trial. *J. Rheumatol.* 2016; 43: 1672–9.

62 Wells AU, Denton CP. Interstitial lung disease in connective tissue disease – mechanisms and management. *Nat. Rev. Rheumatol.* 2014; 10: 728–39.

63 Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. *BMJ* 2016; 352: h6819.

64 Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, Byrson CJ, Byu IH, Selman M, Wells AU et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am. J. Respir. Crit. Care Med.* 2013; 188: 733–48.

65 Moore OA, Goh N, Corte TJ, Rouse H, Hennessy O, Thakkar V, Byron J, Saharj J, Roddy J, Gabbay E et al. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. *Rheumatology (Oxford)* 2013; 52: 155–60.

66 Wiseman AC. Immunosuppressive medications. *Clin. J. Am. Soc. Nephrol.* 2016; 11: 332–43.

67 Meyer KC. Immunosuppressive agents and interstitial lung disease: what are the risks? *Expert Rev. Respir. Med.* 2014; 8: 263–6.

68 Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, Carrero L, Figueroa M; BIO-BADASER Group. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 2005; 52: 1766–72.

69 Juck SS, Liebener ES, Rahman MJ, Choi HK. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum.* 2006; 55: 19–26.

70 Seibold JR, Denton CP, Forst DE, Guilleven L, Rubin LJ, Wells A, Matucci Cerinic M, Riemekasten G, Meriozky P, Chadha-Boreham H et al. Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis. *Arthritis Rheum.* 2010; 62: 2011–8.

71 Cooley L, Dendle C, Wolf J, Teh BW, Chen SC, Boutlis C, Thursky KA. Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematoological and solid malignancies, 2014. *Intern. Med. J.* 2014; 44: 1350–63.

72 Khanna D, Albera C, Fischer A, Khalidi N, Raghu G, Chung L, Chen D, Schiopu E, Tagliaferri M, Seibold JR et al. An open-label, phase II study of the safety and tolerability of Pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUS trial. *J. Rheumatol.* 2016; 43: 1672–9.

73 Hsu V, Denton C, Domsic R, Forst D, Rischmuller M, Stanislav M, Steen V, Distler JW, Korish S, Cooper A et al. Pomalidomide in patients with interstitial lung disease due to systemic sclerosis: a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *J. Rheumatol.* 2018; 45: 405–10.

74 Khanna D, Denton CP, Lin CJ, van Laar JM, Frech TM, Anderson ME, Baron M, Chung L, Frielbeck G, Lakshminarayanan S et al. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). *Arthritis Rheum. Dis.* 2018; 77: 212–20.

75 Reid AB, Chen SC, Worth L. *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients: new risks and diagnostic tools. *Curr. Opin. Infect. Dis.* 2011; 24: 534–44.

76 Daoussis D, Melisaranopoulos K, Sakellaropoulous G, Antonopoulos I, Markatseli TE, Simopoulou T, Georgiou P, Andonopoulous AP, Drosos AA, Sakkas L et al. A multicenter, open-label, comparative study of B-cell depletion therapy with rituximab for systemic sclerosis-associated interstitial lung disease. *Semin. Arthritis Rheum.* 2017; 46: 625–31.

77 Hao Y, Hudson M, Baron M, Carreira P, Stevens W, Rabusa C, Tatibouet S, Carmona L, Joven BE, Huq M et al. Early mortality in a multinational systemic sclerosis inception cohort. *Arthritis Rheumatol.* 2017; 69: 1067–77.

78 Steen VD, Conte C, Owens GR, Medsger TA Jr. Severe restrictive lung disease in systemic sclerosis. *Arthritis Rheum.* 1994; 37: 1283–9.

79 Khanna D, Nagaraja V, Tseng CH, Abtin F, Suh R, Kim G, Wells A, Forst DE, Clements PJ, Roth MD et al. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials. *Arthritis Res. Ther.* 2015; 17: 372.

80 Song JW, Lee CK, Chae EJ, Jang SJ, Colby TV, Kim DS. Clinical course and outcome of rheumatoid arthritis-related usual interstitial pneumonia. *Sarcoidosis Vasc. Diffuse Lung Dis.* 2013; 30: 103–12.

81 Fischer A, Solomon JJ, du Bois RM, Deane KD, Olson AL, Fernandez-Perez ER, Huie TJ, Stevens AD, Gill MB, Rabonvitch AM et al. Lung disease with anti-CCP antibodies but not rheumatoid arthritis or connective tissue disease. *Respir. Med.* 2012; 106: 1040–7.

82 Schnabel A, Reuter M, Biedner J, Richter G, Gross W. Interstitial lung disease in polymyositis and dermatomyositis: clinical course and response to treatment. *Semin. Arthritis Rheum.* 2003; 32: 273–84.

83 Kameda H, Nagasawa H, Ogawa H, Sekiguchi N, Takei H, Tokuhiira M, Amano K, Takeuchi T. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. *J. Rheumatol.* 2005; 32: 1719.

84 Ceribelli A, Fredi M, Taraborelli M, Cavazzana I, Tincani A, Selmi C, Chan JY, Chan EK, Satoh M, Franceschini F. Prevalence and clinical significance of anti-MDA5 antibodies in European patients with polymyositis/dermatomyositis. *Clin. Exp. Rheumatol.* 2014; 32: 891–7.

85 Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes JD, Raghu G, Sauter W, Girard M, Alves M. An open-label, randomized, double-blind, placebo-controlled trial of Pomalidomide in patients with interstitial lung disease due to systemic sclerosis-associated interstitial lung disease. *N. Engl. J. Med.* 2019; 380: 2518–28.

86 Flaherty KR, Wells AU, Cortin V, Devaraj A, Walsh SLF, Inoue Y, Richeldi L, Kolb M, Tetzlaff K, Stowasser S et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. *N. Engl. J. Med.* 2019; 381: 1718–27.

87 Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, Moua T, Crestani B, Wuys WA, Stowasser S et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir. Med.* 2020; 8: 453–60.

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Diagnosis and management of CTD-ILD

100 Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of
102 Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD,
104 Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A,
105 Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D,
(2021)
89 Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E,
92 Reddy K, Beavers K, Hammond S. American Gastroenterological
94 Jee AS, Corte TJ. Current and emerging drug therapies for con-
96 Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in
97 Richardson C, Agrawal R, Lee J, Almagor O, Nelson R, Varga J,

100 Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of
102 Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD,
104 Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A,
105 Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D,
(2021)
89 Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E,
92 Reddy K, Beavers K, Hammond S. American Gastroenterological
94 Jee AS, Corte TJ. Current and emerging drug therapies for con-
96 Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in
97 Richardson C, Agrawal R, Lee J, Almagor O, Nelson R, Varga J,

100 Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of
102 Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD,
104 Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A,
105 Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D,
(2021)
89 Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E,
92 Reddy K, Beavers K, Hammond S. American Gastroenterological
94 Jee AS, Corte TJ. Current and emerging drug therapies for con-
96 Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in
97 Richardson C, Agrawal R, Lee J, Almagor O, Nelson R, Varga J,

100 Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of
102 Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD,
104 Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A,
105 Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D,
(2021)
89 Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E,
92 Reddy K, Beavers K, Hammond S. American Gastroenterological
94 Jee AS, Corte TJ. Current and emerging drug therapies for con-
96 Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in
97 Richardson C, Agrawal R, Lee J, Almagor O, Nelson R, Varga J,

100 Morgan C, Knight C, Lunt M, Black CM, Silman AJ. Predictors of
102 Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD,
104 Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A,
105 Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D,
(2021)
89 Holroyd CR, Seth R, Bukhari M, Malaviya A, Holmes C, Curtis E,
92 Reddy K, Beavers K, Hammond S. American Gastroenterological
94 Jee AS, Corte TJ. Current and emerging drug therapies for con-
96 Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in
97 Richardson C, Agrawal R, Lee J, Almagor O, Nelson R, Varga J,
rheumatoid arthritis-related interstitial lung disease: 10 years’ experience at a single centre. *Rheumatology (Oxford)* 2017; 56: 1348–57.

122 Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, Huie TJ, Krishnamoorthy M, Meehan RT, Olson AL et al. Mycobacterium aviaretei improves lung function in connective tissue disease-associated interstitial lung disease. *J. Rheumatol.* 2013; 40: 640–6.

123 Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N. Engl. J. Med.* 2012; 366: 1968–77.

124 Roubille C, Yamasaki H, Dasgupta P. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. *Semin. Arthritis Rheum.* 2014; 43: 613–26.

125 Alarcón GS, Kremer JM, Macaluso M, Weinblatt ME, Cannon GW, Palmer WR, St Clair EW, Suda T, Asashima H, Asashima M et al. Anti-MDA5 antibody-positive dermatomyositis complicated by autoimmune-associated interstitial lung disease: a review. *Respirology* (2021) :23.

126 Lundberg IE, Miller FW, Tjärnlund A, Bottai M. Diagnosis and classification of idiopathic inflammatory myopathies. *J. Intern. Med.* 2016; 280: 39–51.

127 Hallowell RW, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies and the antisyntethase syndrome: recent advances. *Curr. Opin. Rheumatol.* 2014; 26: 681–9.

128 Hagiwara K, Sato T, Takagi-Kobayashi S, Hasegawa S, Kato K, Kobayashi T et al. Rituximab for refractory interstitial lung disease in patients with dermatomyositis: a single centre experience. *Arthritis Res. Ther.* 2012; 14: R224.

129 Kiely P, Busby AD, Nikiphorou E, Sullivan K, Walsh DA, Weatherall DJ et al. Interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor alpha agents, a retrospective cohort study (Report). *Respirology* 2018; 23: 630–6.

130 Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor [alpha] agents, in a retrospective cohort study (Report). *Arthritis Res. Ther.* 2015; 17: 319.

131 Hallowell R, Horton M. Interstitial lung disease in patients with rheumatoid arthritis: spontaneous and drug induced. *Drugs* 2014; 74: 443–50.

132 Dixon WG, Hyrich KL, Watson KD, Lunt M, Symmons DP. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Ann. Rheum. Dis.* 2010; 69: 1086–91.

133 Koo BS, Hong S, Kim YJ, Kim Y-G, Lee C-K, Yoo B. Mortality in patients with rheumatoid arthritis-associated interstitial lung disease treated with an anti-tumor necrosis factor agent. *Korean J. Intern. Med.* 2015; 30: 104–9.

134 Hagiwara K, Sato T, Takagi-Kobayashi S, Hasegawa S, Shigihara N, Akiyama O. Acute exacerbation of preexisting interstitial lung disease after administration of etanercept for rheumatoid arthritis. *J. Rheumatol.* 2007; 34: 1151–4.

135 Saravanan V, Kelly C. Drug-related pulmonary problems in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2006; 45: 787–9.

136 Lundberg IE, de Visser M, Wither VP. Classification of myositis. *Nat. Rev. Rheumatol.* 2018; 14: 269–78.

137 Lilleker JR, Vencovsky J, Wang G, Wedderburn LR, Diederichsen LP, Schmidt J, Oakley P, Benveniste O, Danielli MG, Danko K et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. *Ann. Rheum. Dis.* 2018; 77: 30–9.

138 Lega JC, Reynaud Q, Belot A, Fabien N, Durieu I, Cottin V. Idiopathic inflammatory myopathies and the lung. *Eur. Respir. Rev.* 2015; 24: 216–38.
interstitial pneumonia cases with psoriasis vulgaris. American Thoracic Society International Congress [Abstract]. Am. J. Respir. Crit. Care Med. 2020; 201: A1589. https://www.asljournals.org/ doi/abs/10.1164/ajccmeference.2012.185.1_MeetingAbstracts. A1589.

198 Har A, Kuwano K, Kawamoto H, Nakagawa H. Psoriasis-associated interstitial pneumonia. Eur. J. Dermatol. 2018; 28: 395–6.

199 Ishikawa G, Acquah S, Salvatore M, Padilla ML. Interstitial lung disease with psoriasis [Abstract]. American Journal of Respiratory and Critical Care Medicine 2017; 195: A7122. https://www.asljournals.org/doi/abs/10.1164/ajccmeference.2017.195.1_MeetingAbstracts.A7122.

200 Peluso R, Iervolino S, Vitelli M, Bruner V, Lupoli G, Di Minno MN. Extra-artericular manifestations in psoriatic arthritis patients. Clin. Rheumatology. 2015; 34: 745–53.

201 Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur. Respir. J. 2019; 53: 1801913.

202 Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, Capener D, Sephton P, Hamilton N, Armstrong GJ et al. ASPIRE registry: assessing the Spectrum of Pulmonary Hypertension identified at a Referre centre. Eur. Respir. J. 2012; 39: 945–55.

203 Launay D, Montani D, Hassoun PM, Cottin V, Le Pavej C, Clerson P, Sitbon O, Jais X, Savale L, Weatherald J et al. Clinical phenotypes and survival of pre-capillary pulmonary hypertension in systemic sclerosis. PLoS One 2013; e0197112.

204 Seeger W, Adir Y, Barbera JA, Champion H, Coghill JG, Cottin V, De Marco T, Galie N, Ghio S, Gibbs S et al. Pulmonary hypertension in chronic lung disease. J. Am. Coll. Cardiol. 2013; 62 (25 Supp): D109–16.

205 Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoepfner MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grunig E et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N. Engl. J. Med. 2015; 373: 834–44.

206 Pulido T, Adzerikh I, Channick RN, Delcroix M, Galie N, Ghofrani HA, Janssa P, Jing ZC, Le Brun FO, Mehta S et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N. Engl. J. Med. 2013; 369: 809–18.

207 Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar J, Landzberg M, Machado RF et al. Updated clinical classification of pulmonary hypertension. J. Am. Coll. Cardiol. 2013; 62 (25 Suppl): D34–41.

208 Sitbon O, Channick R, Chinn KM, Frey A, Gaine S, Galie N, Ghofrani HA, Hoepfner MM, Lang IM, Preis RJ et al. Selepxiqag for the treatment of pulmonary arterial hypertension. N. Engl. J. Med. 2015; 373: 2522–33.

209 Chung I, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, Miller DP, Nicos DJ, Zimmerman RT. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVAIL: identifying systemic sclerosis as a unique phenotype. Chest 2010; 138: 1383–94.

210 Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Van Noordtuga A, Beghetti M et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur. Respir. J. 2015; 46: 903–75.

211 Hadley R, Chan KM. Lung transplantation for connective tissue disease-associated lung disease. In: Dellaripa P, Fischer A, Flaherty K (eds) Pulmonary Manifestations of Rheumatic Disease. New York, Springer, 2014; 179–91.

212 Christle JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbes F, Kirk R, Rahmel AO, Stehlik J, Hertz ML. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. J. Heart Lung Transplant. 2012; 31: 1073–86.

213 Weil D, Benden C, Corrias PA, Dark JH, Davis RD, Keshavjee S, Lederer DJ, Mulligan MJ, Patterson GA, Singer LG et al. A consensuss document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J. Heart Lung Transplant. 2015; 34: 1–15.

214 Gasper WJ, Sweet MP, Golden JA, Hoopes C, Learde LE, Kleinheinz ME, Hays SR, Pattie MG. Lung transplantation in patients with connective tissue disorders and esophageal dysmotility. Dis. Esophagus 2008; 21: 650–5.

215 Takagishi T, Ostrowski R, Alex C, Ryckhlik K, Pelletiere K, Tehrani R. Survival and extrapulmonary course of connective tissue disease after lung transplantation. J. Clin. Rheumatol. 2012; 18: 283–9.

216 Crespo MM, Bermudez CA, Dew MA, Johnson BA, George MP, Bhma J, Morrell M, D’Cunha J, Shigemura N, Richards TJ et al. Lung transplant in patients with scleroderma compared with pulmonary fibrosis. Short- and long-term outcomes. Ann. Am. Thorac. Soc. 2016; 13: 784–92.

217 Delplanque M, Gafosse M, Alt-Outella H, Mercier O, Savale L, Pain O, Mekinian A. Bi-lung transplantation in anti-synthetase syndrome with life-threatening interstitial lung disease. Rheumatology (Oxford) 2018; 57: 1688–9.

218 Holland AE, Fiore JF, Bell EC, Goh N, Westall G, Symons K, Dowman L, Glasper I. Dyspnoea and comorbidity contribute to anxiety and depression in interstitial lung disease. Respirology 2014; 19: 1215–21.

219 Madison JM, Irwin RS. Chronic cough in adults with interstitial lung disease. Curr. Opin. Pulm. Med. 2005; 11: 412–6.

220 Chang JA, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. Chest 1999; 116: 1175–82.

221 Dowman L, Hill CJ, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst. Rev. 2014; (10): CD009322.

222 Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Booter C, Glasper I, Goh NSL, Southcott AM, Burge AT et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax 2017; 72: 610–9.

223 Perez-Boger S, Wuyts W, Barbier V, Demeyer H, Van Mylaem A, Janssens W, Troosters T. Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. Respir. Res. 2018; 19: 182.

224 Bolton CE, Bevan-Smith EF, Blakey JD, Crowe P, Offin SI, Barrow R, Greening NJ, Heslop K, Hull JH, Man WD-C et al. Britsh Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE. Thorax 2013; 68(Suppl. 2): iii1-ii30.

225 McNamara RJ, McKeeough Z, McKenzie DK, Alison JA. Water-based exercise in COPD with physical comorbidities: a randomised controlled trial. Eur. Respir. J. 2013; 41: 1284-91.

226 Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, Hill K, Holland AE, Lareau SC, Man WDC et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am. J. Respir. Crit. Care Med. 2013; 188: e13–64.

227 Nakazawa A, Cox NS, Holland AE. Current best practice in rehabilitation in interstitial lung disease. Ther. Adv. Respir. Dis. 2017; 11: 115–28.

228 Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA et al. Official ATS/ERS/ERS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 2011; 183: 788-824.

229 Hardinge M, Annandale J, Bourne S, Cooper B, Evans A, Freeman D, Green A, Hippolyte S, Knowles V, MacNee W et al. British Thoracic Society guidelines for home oxygen use in adults. Thorax 2015; 70(Suppl. 1): 11–43.

230 Ferrara G, Luppini F, Birring SS, Cerri S, Caminati A, Sköld M, Kreuter M. Best supportive care for idiopathic pulmonary fibrosis: current gaps and future directions. Eur. Respir. Rev. 2018; 27: 170076.

231 Kreuter M, Bendstrup E, Russell AM, Bajwa S, Lindell K, Adir Y, Brown CE, Calligaro G, Cassidy N, Corte TJ et al. Palliative care in...
interstitial lung disease: living well. *Lancet Respir. Med.* 2017; 5: 968–80.

232 Dowman LM, McDonald CF, Bozinovski S, Vlahos R, Gillies R, Pouniots D, Hill CJ, Goh NSL, Holland AE. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. *Respirology* 2022; 22: 957–64.

233 Schaeffer MR, Ryerson CJ, Ramsook AH, Molgat-Seon Y, Wilkie SS, Dhillon SS, Mitchell RA, Sheel AW, Khalil N, Camp PG et al. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. *Eur. Respir. J.* 2017; 49: 1602494.

234 Visca D, Mori L, Tsipouri V, Fleming S, Firouzi A, Bonini M, Pavitt MJ, Alfieri V, Canu S, Bonifazi M et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. *Lancet Respir. Med.* 2018; 6: 759–70.

235 Lindell K, Raghu G. Palliative care for patients with pulmonary fibrosis: symptom relief is essential. *Eur. Respir. J.* 2018; 52: 1802086.

236 Lindell KO. Nonpharmacological therapies for interstitial lung disease. *Curr. Pulmonol. Rep.* 2018; 7: 126–32.

237 Ekström MP, Bornefalk-Hermansson A, Abernethy AP, Currow DC. Safety of benzodiazepines and opioids in very severe respiratory disease: national prospective study. *BMJ* 2014; 348: g445.

238 Gillon S, Clifton II. Breathlessness in palliative care: a practical guide. *Br. J. Hosp. Med.* 2019; 80: 72–7.

239 Simon ST, Higginson IJ, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst. Rev.* 2016; 10: CD007354.

240 Bajwah S, Davies JM, Tanash H, Currow DC, Olyuyase AO, Ekström M. Safety of benzodiazepines and opioids in interstitial lung disease: a national prospective study. *Eur. Respir. J.* 2018; 52: 1801278.

241 Birring SS, Kavanagh JE, Irwin RS, Keogh KA, Lim KG, Ryu JH. Treatment of interstitial lung disease associated cough: CHEST guideline and expert panel report. *Ches* 2018; 154: 904–17.

242 Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 1583–9.

243 Tarrant BJ, Le Maitre C, Romero L, Steward R, Button BM, Thompson BR, Holland AE. Mucoactive agents for chronic, non-cystic fibrosis lung disease: a systematic review and meta-analysis. *Respirology* 2017; 22: 1084–92.

244 Assyag D, Camp PG, Fisher J, Johansson KA, Kolb M, Lohmann T, Manganas H, Morisset J, Ryerson CJ, Shapera S et al. Comprehensive management of fibrotic interstitial lung diseases: a Canadian Thoracic Society position statement. *Can. J. Respir. Crit. Care Sleep Med.* 2018; 2: 234–43.

245 Bourke SJ, Peel ET. Palliative care of chronic progressive lung disease. *Clin. Med. (Lond.)* 2014; 14: 79–82.

246 Swigris JJ, Fairclough DL, Morrison M, Make B, Kozora E, Brown KK, Wamboldt FS. Benefits of pulmonary rehabilitation in idiopathic pulmonary fibrosis. *Respir. Care* 2011; 56: 783–9.

247 Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, Khalil N, Collard HR, Garvey C. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. *Respir. Med.* 2014; 108: 103–10.

248 van Manen MJG, Geelhoed JJM, Tak NC, Wijsenbeek MS. Optimizing quality of life in patients with idiopathic pulmonary fibrosis. *Thor. Adv. Respir. Dis.* 2017; 11: 157–69.

249 Wallaert B, Duthoit L, Drumez E, Behal H, Wemeau L, Chenèvasses C, Grosbois J-M. Long-term evaluation of home-based pulmonary rehabilitation in patients with fibrotic idiopathic interstitial pneumonias. *Eur Open Res.* 2019; 5: 00045-2019.

250 Ley B, Torgerson DG, Oldham JM, Adegunsoye A, Liu S, Li J, Elcker BM, Henry TS, Golden JA, Jones KD et al. Rare protein-altering telomere-related gene variants in patients with chronic hypersensitivity pneumonitis. *Am. J. Respir. Crit. Care Med.* 2019; 200: 1154–63.

251 Stuart BD, Lee JS, Kozlitina J, Noth I, Devine MS, Glazer CS, Torres F, Kaza V, Giord CE, Jones KD et al. Effect of telomere length on survival in patients with idiopathic pulmonary fibrosis: an observational cohort study with independent validation. *Lancet Respir. Med.* 2014; 2: 557–65.
