Connective tissue diseases, multimorbidity and the ageing lung

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ABSTRACT Connective tissue diseases encompass a wide range of heterogeneous disorders characterised by immune-mediated chronic inflammation often leading to tissue damage, collagen deposition and possible loss of function of the target organ. Lung involvement is a common complication of connective tissue diseases. Depending on the underlying disease, various thoracic compartments can be involved but interstitial lung disease is a major contributor to morbidity and mortality. Interstitial lung disease, pulmonary hypertension or both are found most commonly in systemic sclerosis. In the elderly, the prevalence of connective tissue diseases continues to rise due to both longer life expectancy and more effective and better-tolerated treatments. In the geriatric population, connective tissue diseases are almost invariably accompanied by age-related comorbidities, and disease- and treatment-related complications, which contribute to the significant morbidity and mortality associated with these conditions, and complicate treatment decision-making. Connective tissue diseases in the elderly represent a growing concern for healthcare providers and an increasing burden of global health resources worldwide. A better understanding of the mechanisms involved in the regulation of the immune functions in the elderly and evidence-based guidelines specifically designed for this patient population are instrumental to improving the management of connective tissue diseases in elderly patients.

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Age does not depend upon years, but upon temperament and health. Some men are born old, and some never grow so. Tryon Edwards

Introduction

The term connective tissue disease (CTD) refers to a large and heterogeneous group of immunologically mediated disorders characterised by inflammation, tissue damage and abnormal repair, often leading to degeneration of the target organ, replacement by fibrotic tissue and loss of function. These disorders are multifactorial in origin, with a complex interaction between genetic and environmental factors contributing to their development [1]. CTDs are often complicated by comorbidity [2], which is defined as "the existence or occurrence of any distinct additional entity during the clinical course of a patient who has the index disease under study" [3]. Accordingly, comorbidity includes: 1) conditions directly pathophysiologically linked to the index disease (*e.g.* cardiovascular disease following rheumatoid arthritis); 2) complications resulting from treatment of the index disease (*e.g.* glucocorticoid-induced diabetes mellitus); and 3) conditions indirectly linked to the disease or its management (*e.g.* infection in rheumatoid arthritis) [4]. Comorbidities are associated with increased use of multiple therapies and, therefore, higher risk of drug interactions. However, multimorbidity, defined as the coexistence of two or more chronic diseases in the same individual, irrespective of whether the disease started before or after the onset of the index disease, is far more common in CTDs, particularly in an ageing patient population [5]. In multimorbidity, no index disease is defined and all morbidities are regarded of equal importance. Both comorbidities and multimorbidities impact significantly on patients' health as they reduce quality of life and life expectancy, and add considerable complexity to patient care [4]. Not surprisingly, greater healthcare utilisation accompanies this higher chronicity burden [6]. Because treatment options for CTDs have become increasingly effective (and better tolerated), patient survival has improved. As a consequence, the impact of comorbid conditions in individuals suffering from these disorders has become a growing concern for healthcare providers.

The lung is a frequent target of autoimmune-mediated injury in patients with CTDs by virtue of its abundant connective tissue and blood supply, and pulmonary involvement is a leading cause of morbidity and mortality in this setting. All compartments can be affected (*e.g.* airways, lung parenchyma, vasculature and pleura), though in various degrees and combinations depending on the underlying disease [7] (tables 1 and 2).

CTDs in the elderly: prevalence and disease burden

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by erosive inflammatory polyarthropathy with symmetric polyarthritis. RA affects approximately 1% of the population worldwide, and women are twice as likely as men to be affected (table 3) [8]. While RA can occur in individuals of any age, with the peak incidence being observed between the fourth and sixth decade, its incidence

TABLE 1 Types of lung involvement in connective tissue diseases

Primary manifestations
Pleural involvement
Pleurisy, effusion/thickening
Airway disease
Cricoarytenoid and tracheal involvement
Bronchiectasis, bronchiolitis
Vascular involvement
Pulmonary hypertension
Vasculitis
Parenchymal lung disease
Interstitial lung disease
Diffuse alveolar haemorrhage
Acute pneumonitis
Rheumatoid nodules
Secondary manifestations
Infection
Drug toxicity
Malignancy
Thromboembolism

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TABLE 2 Common pulmonary manifestations in connective tissue diseases

Manifestation	RA	SSc	SS	SLE	PM/DM	MCTD	AS
Pleural disease[#]	++	–	+	+++	–	+	–
Airway disease[¶]	++	–	++	+	–	+	–
Interstitial lung disease	++	+++	++	+	+++	++	+
DAD	+	+	+	++	+	+	–
DAH and capillaritis	+	–		++	–	–	–
OP	++	+	+	+	+++	+	–
NSIP	+	+++	++	++	+++	++	+
UIP	+++	+	+	+	+	+	–
LIP	+	–	+++	+	–	–	–
Vascular disease	+	+++	+	+	+	++	–
Pulmonary hypertension	+	+++	+	+	–	+	–
Parenchymal nodules	+	–	–	–	–	–	–
Apical fibrobullous disease	+	–	–	–	–	–	+++
Respiratory muscle dysfunction	–	–	–	+++	++	+	–
Aspiration pneumonia	–	+++	–	–	+	+	–

The signs indicate the frequency of each manifestation (*i.e.* –: rare/not described; +: low prevalence; ++: medium prevalence; +++: high prevalence). RA: rheumatoid arthritis; SSc: systemic sclerosis; SS: Sjögren's syndrome; SLE: systemic lupus erythematosus; PM: polymyositis; DM: dermatomyositis; MCTD: mixed connective tissue disease; AS: ankylosing spondylitis; DAD: diffuse alveolar damage; DAH: diffuse alveolar haemorrhage; OP: organising pneumonia; NSIP: nonspecific interstitial pneumonia; UIP: usual interstitial pneumonia; LIP: lymphocytic interstitial pneumonia. [#]: inflammation, fibrosis or effusion; [¶]: inflammation, obstruction or lymphoid hyperplasia.

continues to increase with age, while its prevalence becomes almost equal in both sexes [9]. The term "elderly-onset RA" refers to the *de novo* development of the disease at age 60 years or older, yet in most patients in this age group, RA represents the persistence of a disease that manifested clinically at a younger age (young-onset RA). Compared with young-onset RA, elderly-onset RA is characterised by a higher frequency of acute onset and more frequent involvement of large joints [10] (table 4).

Systemic sclerosis

Systemic sclerosis (SSc) is an uncommon disease characterised by endothelial and epithelial cell injury, fibroblast dysregulation, and immune system abnormalities leading to systemic inflammation, fibrosis of target organs and vascular damage [11]. Clinical forms range from mild, limited skin involvement (limited cutaneous SSc) to widespread skin thickening and severe internal organ involvement (diffuse cutaneous SSc). Early in life, the female/male ratio is 7/1 but this narrows to 2/1 after the fifth decade [12]. The disease is more common among black people. Pulmonary involvement, in the form of either pulmonary vascular disease or interstitial lung disease (ILD), is a common complication and a major cause of death in patients with SSc (table 5) [13, 14]. Although SSc affects adults of all ages (with a peak age of onset between 40 to 50 years), a number of studies have reported newly diagnosed cases in the sixth, seventh and eighth decades of life [15–17]. In a large cohort of SSc patients (n=2300), among those with late-onset disease (n=216, 9%), 105 (49%) had onset between 65–70 years, 68 (31%) between 70–75 years, 36 (17%) between 75–80 years and seven (3%) had onset at greater than 80 years of age [18]. In a North American SSc cohort study, among white patients, the peak incidence of SSc was between 65 and 74 years in women and >75 years in men [19]. While patients who develop SSc later in life (⩾65 years) may express the entire clinical spectrum of the disease, those with late-onset SSc tend to display a more atypical disease course, often influenced by comedication and comorbidities [20], and are at greater risk of pulmonary hypertension (PH), cardiac disease, muscle weakness and renal impairment than those with a younger-age onset disease [18]. Moreover, older age at diagnosis is associated with a decreased survival, related to both disease severity and comorbid conditions, when compared to a population matched for age, sex and race [19, 21].

Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic autoimmune disorder characterised by progressive lymphocytic infiltration of exocrine glands, mainly salivary and lacrimal glands, leading to dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). The disease, which can occur either in isolation (primary SS) or in the setting of another established CTD (secondary SS) [22], primarily affects women (female/male ratio 9/1),

TABLE 3 Established and putative risk factors for the development of the most common connective tissue diseases

Disease	Established risk factors	Putative risk factors
RA	Female sex Genetic factors (*HLA-DRB*, *PTPN22*, *STAT4* and *TRAF1/C5*) Smoking[#] Family history of RA	Low testosterone levels in males Changes in the female hormonal environment (pregnancy, breast feeding or use of oral contraceptives) Silica dust exposure Diets high in caffeine, low in antioxidants and high in red meat Obesity Bacterial and viral infection.
SSc	Female sex African-American ethnicity Genetic factors (*HLA-DR5, -DQB1* and *-DPA1/B1*, *IRF5*, and *PTPN22*) Microchimaerism Drugs (carbidopa and bleomycin) Family history of SSc Environmental agents (*e.g.* silica dust, petroleum-based products, vinyl chloride, contaminated rapeseed oil and L-tryptophan)	Diabetes Genetic factors (*CTGF* and *TGFB*) Smoking[¶] Bacterial and viral infection
SS	Age (>40 years) Female sex (particularly women with one or more pregnancies) Genetic factors (*HLA-DR52, -DR3, -DR5, -DRB1*15, -DQ2* and *-B8*) Pre-existing rheumatological diseases (RA and SLE) Family history of autoimmune disease	Viruses (EBV, HTLV-1, HHV-6, HIV, HCV and CMV)
SLE	Female sex (the risk is highest in women of childbearing age) Hispanic or African-American ethnicity Familial history of SLE (the risk is 20 times higher if an immediate family member has SLE) Genetic factors (*HLA-DR2, -DR3, C2, C4* and *C1q*; *TREX1, IRF5,* and *APRIL*) Environmental triggers (sunlight, chemicals) Smoking[¶] Drugs (hormone replacement therapy and oral contraceptives)	
PM/DM	Genetic factors (*HLA-DRB1*0301* and *-DQA1*0501*) Drugs (hydroxyurea, statins and penicillamine) Environmental triggers (ultraviolet light)	*TNF* –308A allele Silicone breast implants or collagen injections Viral (HTLV-1, HIV, Coxsackie virus, parvovirus and echovirus) and parasitic infection Smoking[+]
MCTD	Genetic factors (*HLA-DR2* and *-DR4*)	Female sex Family history of MCTD
AS	Male sex Genetic factors (*HLA-B27*) Smoking[¶] Family history of AS	

RA: rheumatoid arthritis; SSc: systemic sclerosis; SS: Sjögren's syndrome; SLE: systemic lupus erythematosus; PM: polymyositis; DM: dermatomyositis; MCTD: mixed connective tissue disease; AS: ankylosing spondylitis; EBV: Epstein–Barr virus; HTLV-1: human T-lymphotropic virus-1; HHV-6: human herpes virus-6; HCV: hepatitis C virus; CMV: cytomegalovirus. [#]: also a risk factor for the development of interstitial lung disease in patients with pre-existing RA; [¶]: also a risk factor for the development of more severe disease; [+]: associated with the presence of anti-Jo-1 antibodies.

with an estimated prevalence between 0.5% and 1% [23]. Although the mean age of onset of SS is usually in the fourth to fifth decade, rates of onset of 6% in individuals over 65 years of age [24] and 14% in subjects aged 70–87 years [25] have also been reported. Elderly patients with SS seem to have a more benign disease course [26]. Differentiating SS from alternative causes of sicca syndrome, such as age- and medication-related dehydration and xerostomia, may be challenging in this patient population.

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TABLE 4 Distinguishing features of connective tissue diseases in the elderly (other than comorbidities)

Disease	Proportion of cases diagnosed after the age of 65 years[#]	Distinguishing features in the elderly
RA	Approximately 30%[¶] Approximately 2% of persons aged 60 years and older are diagnosed with RA	Male sex Acute onset Large joints (*e.g.* shoulders) more commonly involved Persistently active disease Rapid functional decline Rheumatoid factor less frequently detected
SSc	Approximately 10%	Higher prevalence of anticentromere antibodies Increased risk of pulmonary hypertension, muscle weakness, renal impairment and cardiac disease Reduced risk of digital ischaemia and less severe Raynaud's phenomenon
SS	Between 5% and 10%	Often difficult to distinguish from age-related exocrine gland pathology and drug-induced ocular and oral dryness Sex distribution, disease duration, ocular and oral symptoms, and diagnostic test positivity not significantly different between adult- and early-onset primary SS
SLE	Approximately 10–20%	More benign disease Higher prevalence of serositis, sicca syndrome, lung involvement and drug-induced lupus Lower prevalence of malar rash, discoid lupus and glomerulonephritis Lower prevalence of anti-double-stranded DNA and hypocomplementaemia Higher rate of positive rheumatoid factor and anti-Ro/SSA and anti-La/SSB
PM/DM	<10%	Difficult to distinguish from age-related fatigue or joint pain Higher erythrocyte sedimentation rate, and levels of C-reactive protein, fibrinogen and ferritin Oesophageal involvement common Higher risk of malignancy (particularly with DM)
MCTD	Rare	Poorly defined
AS	Uncommon	More severe disease Cervical spine involvement and arthritis of the upper and lower limbs more common Radiological abnormalities difficult to distinguish from changes induced by ageing

RA: rheumatoid arthritis; SSc: systemic sclerosis; SS: Sjögren's syndrome; SLE: systemic lupus erythematosus; PM: polymyositis; DM: dermatomyositis; MCTD: mixed connective tissue disease; AS: ankylosing spondylitis. [#]: prevalence of CTD in individuals older than 65 years has not been systematically evaluated; the values in this table represent estimates as published data often refer to "elderly-onset" or "late-onset" disease, which does not necessarily correspond to disease occurring in subjects older than 65 years of age; [¶]: elderly-onset RA is defined as RA with onset at age 60 years or older.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a relatively rare but frequently disabling disorder characterised by autoantibody positivity, immune-mediated damage to virtually every organ system, and a typically waxing and waning course [27]. Although a wide array of laboratory abnormalities may be found in SLE, most characteristic is the demonstration of antibodies reactive to nuclear and extractable nuclear antigens, including anti-nuclear antibodies (ANAs), anti-double-stranded DNA (dsDNA) and anti-Smith, which are part of the diagnostic criteria [28]. SLE has a prevalence of 15–124 per 100 000 of the population worldwide and occurs predominantly in women of childbearing age (female/male ratio 6/1) [29]. However, late-onset SLE (*e.g.* disease developing beyond 50–65 years of age) occurs in 3–18% of patients [30]. Arthritis, fever, serositis, sicca syndrome, Raynaud's phenomenon, lung disease and neuropsychiatric symptoms are more prevalent in elderly patients with SLE, whereas malar rash, discoid lupus and glomerulonephritis are less common in this patient subset compared with younger patients [31]. Notably, fever, lymphadenopathy, weight loss, arthralgia and fatigue (all common presenting symptoms) may also be due to other conditions more prevalent in the ageing population, such as endocrinopathy, infections or malignancy.

TABLE 5 Major causes of death and predictors of worse outcome in connective tissue diseases

Disease	Major causes of death		Predictors of worse outcome
	Direct or indirect disease complications[#]	Comorbidities	
RA	Infection (mainly pneumonia) Pulmonary fibrosis Osteoporosis/fractures Cancer	Cardiovascular disease (*e.g.*, ischaemic heart disease, atrial fibrillation and heart failure) Cerebrovascular disease	Male sex Older age Worse physical disability Extra-articular manifestations Positive rheumatoid factor Pulmonary fibrosis Corticosteroid use Comorbidities
SSc	Pulmonary hypertension Pulmonary fibrosis Scleroderma renal crisis Cancer	Liver disease Inflammatory bowel disease Multiple sclerosis Neuropsychiatric disorders	Older age at onset Male sex Diffuse skin involvement Scleroderma renal crisis Pulmonary fibrosis Pulmonary hypertension Anti-topoisomerase 1 (Scl-70) and anti-U1 RNP antibodies
SS	Lymphoproliferative disorders	Cardiovascular, endocrine, gastrointestinal and psychological disorders	Low C3 and/or C4 levels at the time of diagnosis
SLE	Infection Renal and cardiovascular disease Haematological manifestations Cancer Osteoporosis/fractures	Cardiovascular and cerebrovascular disease (*e.g.* hypertension, atherosclerosis and thromboembolic events)	Female sex Disease duration <1 year Disease onset after the age of 50 years Older age Black/African-American race Haematological manifestations Active disease Immunosuppressive therapy
PM/DM	Aspiration pneumonia Cancer (particularly in DM)	Cardiovascular disease (*e.g.* hypertensions and ischaemic heart disease) Venous thromboembolism Diabetes	Female sex Older age at onset Shorter disease history Failure to induce remission Smoking Dysphagia
MCTD	Pulmonary hypertension Pulmonary fibrosis Scleroderma renal crisis Infection	Cardiovascular and thromboembolic events	Pulmonary hypertension Evolution into SLE or SSc
AS	Musculoskeletal abnormalities (spinal fractures and cervical subluxation) Secondary amyloidosis Infection	Cardiovascular and cerebrovascular disease Bowel, liver and haematological disease Psychiatric disorders	Permanent pain Ongoing disease activity Disease manifestations in hips, peripheral joints, entheses, uvea and heart Limitation of spinal mobility Osteoporosis Development of amyloidosis

RA: rheumatoid arthritis; SSc: systemic sclerosis; SS: Sjögren's syndrome; SLE: systemic lupus erythematosus; PM: polymyositis; DM: dermatomyositis; MCTD: mixed connective tissue disease; AS: ankylosing spondylitis; RNP: ribonucleoprotein. [#]: complications and comorbidities may be difficult to distinguish; therefore, this separation is somewhat artificial and should be viewed as such.

Polymyositis/dermatomyositis

Polymyositis (PM) and dermatomyositis (DM) are rare idiopathic inflammatory myopathies characterised by symmetrical proximal muscle weakness, raised serum muscle enzymes, and muscle biopsy and electromyography (EMG) findings consistent with myositis [32, 33]. Patients with DM also have a characteristic skin rash. The prevalence of PM/DM is estimated to be approximately one per 100 000 [34]. These diseases, which are twice as common in females, can occur at any age but have a bimodal incidence

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pattern with a first peak in childhood (10–15 years of age) and a second between 35 and 65 years of age [35]. A number of studies have found a high prevalence of PM/DM in elderly patients. While clinical manifestations generally do not differ significantly across age groups, elderly patients have higher rates of infections, malignancies and mortality [36]. In addition, older patients are more likely to have normal creatine kinase levels, which, together with the nonspecific presenting symptoms (*e.g.* general weakness) and the difficulty in interpreting EMG findings in this patient subgroup, may delay the diagnosis [37, 38].

Mixed connective tissue disease

The term "mixed connective tissue disease" (MCTD) refers to a systemic autoimmune disorder characterised by overlapping features between SLE, SSc, PM/DM and RA, mainly Raynaud's phenomenon, polyarthritis, puffy fingers, muscle weakness, ILD and oesophageal dysmotility, along with positive antibodies against the U1 small nuclear ribonucleoprotein autoantigen [39, 40]. Due to the lack of universally accepted classification or diagnostic criteria for MCTD, limited epidemiological data exist. However, MCTD appears to have a prevalence of approximately four per 100 000, with female predominance [41]. Mean age at diagnosis is around 35 years, whereas MCTD is rare after age 60 years [41].

Ankylosing spondylitis

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease of the joints and axial skeleton that primarily affects young males (male/female ratio 2.5/1) [42]. The disease, which is estimated to affect 0.1% of the general population, usually presents with insidious onset of back pain and stiffness during adolescence and early adulthood [43]. Disease onset after 55 years of age is uncommon [44]. In the elderly, radiological features of AS may be difficult to distinguish from changes induced by ageing, such as osteoporosis, osteoarthritis and disc arthrosis. Moreover, other conditions more common in elderly patients (*e.g.* RA and polymyalgia) may present in a similar fashion. Compared with young-onset disease, elderly patients with AS tend to present more commonly with moderate involvement of the axial skeleton, cervical spine pain, oligoarthritis of the lower limbs with pitting oedema, severe illness and marked elevation of laboratory parameters of inflammation [45–47].

Undifferentiated connective tissue disease

The term "undifferentiated connective tissue disease" (UCTD) is used to indicate patients who exhibit signs, symptoms and serological abnormalities suggestive of an underlying autoimmune disorder but who do not fulfil all diagnostic criteria for any of the defined CTDs [48]. UCTD is more common in females and in patients in their third to fifth decade of life [49, 50], and tends to either evolve into a definite CTD (in 20–40% of cases) or remain undifferentiated [51].

In the rheumatological literature, UCTD is a mild disease complicated by pulmonary fibrosis in <1% of cases [52]. However, a large minority of patients with ILD meet some, but not all, diagnostic criteria for a definite CTD [53–55]. The term "interstitial pneumonia with autoimmune features" has recently been proposed to describe this subset of patients whose clinical, radiological and pathologic features are highly heterogeneous [56]. Uncertainty remains, however, over how best to follow, treat and conduct research in this patient population.

Utility of serological testing in patients with suspected CTD

Serological testing can help make the diagnosis of CTD as an adjunct to a comprehensive history and physical examination. Indeed, very few tests are specific for a certain disease. However, the ANA test, which detects autoantibodies that bind to a variety of nuclear antigens, is commonly used in the initial evaluation of patients with suspected CTD. In the appropriate clinical setting, ANA testing is useful in establishing a diagnosis of SLE as nearly all SLE patients have a positive ANA test (sensitivity >95%) (table 6). However, a positive test *per se* is not diagnostic for SLE (specificity <60%) as these antibodies can be found in other autoimmune diseases (*e.g.* autoimmune hepatitis and primary biliary cirrhosis), in chronic infectious diseases and in healthy individuals, especially the elderly. Conversely, a negative ANA test makes a diagnosis of SLE highly unlikely. A positive ANA test is found in approximately 85% of patients with SSc [57] and 80% of patients with primary SS [61], but its specificity for these diseases is 54% and 52%, respectively. ANA testing should therefore be reserved for patients with high suspicion for CTD. The staining pattern of ANA seen on indirect immunofluorescence (*e.g.* homogeneous and diffuse, speckled, centromeric, and nucleolar), which is determined by the target antigen, is neither sensitive nor specific (table 6). Therefore, identification of the pattern-associated antibodies and correlation with clinical assessment are required in order to further differentiate between the distinct types of CTDs.

Rheumatoid factor (RF) is commonly used in the initial evaluation of patients with suspected RA. However, its sensitivity for RA ranges between 50% and 85%, and tends to increase over time, as some patients are initially RF negative only to seroconvert later. Around 15% of patients never have RF

TABLE 6 Prevalence of selected autoantibodies in connective tissue diseases (CTDs)

Antibodies	Disease	Prevalence %	Associations/comment
ANA	SLE	>95	
	MCTD	95	
	SSc	70–90	
	PM/DM	40–60	
	SS	50–80	
	RA	40–50	
Pattern			
Homogeneous and diffuse			
Anti-histone	SLE	60–80	Present in >95% of patients with drug-induced SLE
Anti-dsDNA	SLE	40–60	Highly specific Severe disease and renal involvement Titres tend to associate with disease activity
Speckled			
Anti-Sm	SLE	25–30	Highly specific
Anti-topoisomerase 1	SSc	20–25	Increased risk of diffuse cutaneous involvement and pulmonary fibrosis
Anti-U1 RNP	MCTD	100	Present at high titre in all patients with MCTD, often before disease onset At lower titre may be found also in SLE, RA and SSc
	SLE	30–40	
Anti-U3 RNP	SSc	10–15	
Anti-SS-A/Ro	SS	60–75	Extraglandular involvement (*e.g.* vasculitis, lymphadenopathy and nephritis) Rarely found in healthy individuals
	SLE	40–50	Photosensitivity, cutaneous vasculitis and ILD
Anti-SS-B/La	SS	40–50	Rarely present in other CTDs
	SLE	15–20	Rarely present in other CTDs
Centromeric			
Anti-centromere	lcSSc	30–35	Increased risk of PH Reduced risk of pulmonary fibrosis Rarely found in patients with other CTDs or in healthy persons
Nucleolar			
Anti-RNA polymerase	SSc	25–30	Low incidence of pulmonary fibrosis
Anti-PM-Scl	SSc	7–10	Younger age at disease onset Skeletal muscle involvement Inflammatory arthritis
Cytoplasmic staining			
Anti-(t)RNA synthetases	PM/DM	25 to 40 (mainly anti-Jo-1)	High risk of ILD, Raynaud's phenomenon and mechanic's hands
RF	RA	50–85	May be negative in early-phase RA High titres strongly predict severe disease (*e.g.* ILD and vasculitis) May be present also in SLE and SS
Anti-CCP	RA	30–60	More specific than RF for RA May be present years before disease onset and while RF is negative Increased risk of progressive joint damage May be present also in SLE and SS

More than one pattern can be present in a patient. ANA: anti-nuclear antibody; ds: double-stranded; Sm: Smith; RNP: ribonucleoprotein; t: transfer; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; SLE: systemic lupus erythematosus; MCTD: mixed connective tissue disease; SSc: systemic sclerosis; PM: polymyositis; DM: dermatomyositis; SS: Sjögren's syndrome; RA: rheumatoid arthritis; lc: limited cutaneous; PH: pulmonary hypertension; ILD: interstitial lung disease. Data from [57–60].

positivity and up to 5% of healthy individuals can be RF positive (this rate increases with age) [58]. Accordingly, this test should only be requested when the diagnosis of RA is strongly suspected (*e.g.* in the presence of joint swelling, synovitis or effusions). Conversely, in elderly subjects with mild age-related joint abnormalities, RF may be falsely positive, thus leading to an erroneous diagnosis of RA. Compared to RF, anti-cyclic citrullinated peptide (anti-CCP) antibodies are as sensitive but more specific for RA (90% to 95%) [62]. In addition, these antibodies are more likely to be present early in the disease course and may be helpful in suggesting the diagnosis in patients with a negative RF [63]. Serial measurement of RF or anti-CCP antibodies over time is of limited value for monitoring disease activity.

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A tentative list of autoantibodies useful in assessing CTD is provided in table 6. However, these laboratory tests should never circumvent the need for a thorough history and careful clinical examination, which arguably remain the best screening tools for CTDs.

Pulmonary involvement in CTD

Screening and evaluation of ILD

At present, it is unclear how and how often patients with CTD should be screened for lung involvement. Initial evaluation should include a comprehensive clinical, functional and radiological assessment. At presentation, patients with CTD-associated lung involvement are often asymptomatic, at least early in the disease course, or report nonspecific symptoms (*e.g.* dyspnoea on exertion, cough or fatigue), which elderly patients tend to attribute initially to deconditioning and age. Respiratory symptoms can be due to pulmonary (*e.g.* pleuritis and pleural effusion, vascular disease, airway disease, or ILD) and nonpulmonary causes (*e.g.* anaemia, chest wall involvement, joint disease or muscle weakness), as well as to opportunistic infections and malignancy, which are more frequent in chronically immunosuppressed patients. In addition, each CTD can be associated with multiple pulmonary manifestations (table 2). Dyspnoea, typically the first and predominant respiratory symptom, can be quantified using detailed questionnaires, although none has been validated in CTD [64], yet a baseline measurement of dyspnoea represents a valuable tool to identify worsening symptoms and function over time [65]. Physical examination is often unremarkable but may reveal fine bibasilar, end-inspiratory, "velcro-like" crackles, which can precede the development of clinically overt ILD [66] and should prompt further investigations. Pulmonary function tests (PFTs) are commonly performed to screen patients with CTD for lung involvement (as well as to monitor disease activity and progression in patients with established lung involvement), although normal physiology does not exclude mild lung disease. Reduced diffusing capacity of the lung for carbon monoxide (*D*LCO), though nonspecific, is often the first physiologic manifestation of ILD, whereas a restrictive ventilatory defect is characteristic of more advanced disease [67, 68]. Functional assessment, mostly performed by measuring 6-min walk distance (6MWD), may unmask exertional desaturation in patients with normal resting arterial saturation, thus providing additional information beyond standard PFTs [69]. In SSc, specific serological findings (*e.g.* anti-topoisomerase antibodies (ATAs)) and pattern of skin involvement (*e.g.* diffuse cutaneous disease) are associated with an increased risk of developing ILD [70, 71].

Chest radiography is neither sensitive nor specific for ILD [72], although occasionally it can identify parenchymal abnormalities suggestive of ILD or other CTD-associated pulmonary manifestations (*e.g.* pleural effusion). High-resolution computed tomography (HRCT) is more sensitive than chest radiography in diagnosing ILD in patients with CTD and may provide important prognostic information (*e.g.* a radiological pattern of usual interstitial pneumonia (UIP) is highly specific for histopathological UIP in patients with RA) [73], and is associated with a poor prognosis [74]. However, HRCT is not routinely used as a serial screening procedure in asymptomatic patients with CTD [65]. Bronchoalveolar lavage has no clear role in the assessment and evaluation of CTD-associated ILD, whereas it is useful in ruling out alternative diagnoses such as drug reactions, diffuse alveolar haemorrhage and opportunistic infection [75, 76]. Surgical lung biopsy is generally not performed in patients with established CTD due to both significant risks of complications, particularly in elderly patients, and lack of clear evidence that the histopathological pattern should influence disease management.

Screening modalities for CTD-related PH

PH is a frequent complication of CTD, particularly SSc. Indeed, SSc accounts for more than 70% of cases of CTD-related PH [77, 78]. As with other forms of PH, right heart catheterisation (RHC) remains the diagnostic gold standard [79]. However, RHC is invasive, and alternative techniques have been used in this setting [80]. Transthoracic echocardiography (TTE) is a good screening test for suspected PH, and may be also useful for monitoring disease course and response to treatment [81]. However, TTE is reliable in the presence of severe PH but is not as sensitive in mild-to-moderate PH [14, 81]. Universally agreed upon parameters and thresholds for the diagnosis (or exclusion) of PH are not available. However, a recently developed algorithm for determining the need for RHC in SSc patients based on tricuspid regurgitation velocity and right atrium area has been shown to minimise missed diagnoses (*e.g.* false-negative rate of approximately 4%) and identify milder disease, although this algorithm does not apply to patients with a *D*LCO $\geqslant$60% predicted [79, 82]. Echocardiographic screening for the detection of PH is recommended annually in asymptomatic patients with SSc but only in the presence of symptoms in other CTDs [79]. Pulmonary function parameters may also be useful in predicting PH. Indeed, patients with limited cutaneous SSc and PH may have an isolated reduction of *D*LCO years before the diagnosis [83]. In addition, a threshold of *D*LCO of 50% predicted has a high specificity, though a low sensitivity, for SSc-PH [81]. However, a *D*LCO >60% reliably excludes PH [84]. Biomarkers, such as N-terminal pro-brain natriuretic

peptide, may help identify or rule out SSc-PH, thus providing additional value in screening [85]. An important limitation of screening, however, is that it does not discriminate between SSc-associated pulmonary arterial hypertension (PAH) and forms of PH that are less amenable to treatment, such as SSc-related left heart dysfunction leading to post-capillary PH, chronic thromboembolic disease and pulmonary veno-occlusive disease (PVOD).

Pulmonary manifestations of individual CTDs

Rheumatoid arthritis

Pulmonary disease is a major source of morbidity and mortality in RA [86]. Indeed, while overall mortality rates in RA have decreased over time, those associated with RA-ILD have increased significantly in older age groups [86]. A wide range of pulmonary manifestations are associated with RA, including ILD, airway disease (bronchiectasis, bronchiolitis and cricoarytenoid arthritis), pleural disease (effusions and thickening), rheumatoid pulmonary nodules (usually associated with extrapulmonary nodules), drug-induced (*e.g.* methotrexate, gold, sulfasalazine or penicillamine) pulmonary disease, pulmonary infections, Caplan's syndrome (cavitating pulmonary rheumatoid nodules associated with coalminers' pneumoconiosis) and, rarely, pulmonary vasculitis [87]. ILD is usually diagnosed in patients with well-established disease but it may precede arthritis and other rheumatological complaints in up to 20% of cases [88]. Risk factors for the development of RA-ILD include older age, male sex and a history of cigarette smoking [87]. The pathogenesis of RA-associated pulmonary fibrosis appears to be similar to that of many of the CTDs, with alveolar epithelial injury (triggered by environmental pathogens or inflammation) resulting in damage to lung tissue and initiation of aberrant repair pathways [1, 89]. However, in contrast to the other CTDs, the pathology of RA-ILD shows a preponderance of the UIP pattern [90], although certain features, such as lymphoid hyperplasia and plasma cell infiltration, usually suggest the diagnosis [91].

The term "combined pulmonary fibrosis and emphysema" (CPFE) syndrome refers to a recently defined smoking-related syndrome characterised by the coexistence of upper lobe emphysema and lower lobe fibrosis (mainly of the UIP pattern) [92]. Distinguishing physiological features include preserved lung volumes, severely impaired D_{LCO} and hypoxaemia on exercise. CPFE is a strong determinant of secondary PH, which negatively affects survival [93, 94]. The incidence of CPFE remains unknown but it has been reported to be as high as 35% amongst patients with idiopathic pulmonary fibrosis (IPF) [95, 96]. In a study of 150 consecutive RA patients, 28 (19%) had ILD, including 12 who also had emphysematous bullae [97]. In another study, emphysema was observed in 15 out of 63 patients with RA and was significantly more frequent among those with a radiological pattern of UIP [98]. Earlier recognition of lung involvement in the context of a systemic disease is likely to account for the milder lung disease in patients with CTD-associated CPFE compared to "idiopathic" CPFE [99].

Systemic sclerosis

Pulmonary involvement is a common complication (with prevalence estimates of up to 80%) and the leading cause of morbidity and mortality in patients with SSc [100]. Clinically significant ILD is present in approximately 25% of all SSc patients [101] but its prevalence varies greatly based on several factors, including disease subset and autoantibody profile. Specifically, patients with diffuse cutaneous SSc or ATAs (anti-Scl70, which are found in 12% to 40% of patients) are at higher risk for developing ILD, whereas patients with limited cutaneous SSc or anti-centromere antibodies (which are present in 40% to 70% of cases) less commonly develop ILD but are at increased risk of SSc-PH [102]. Notably, these serological markers are almost mutually exclusive [103]. HRCT plays an important role in determining the pattern and extent of ILD in SSc. The most common pattern is nonspecific interstitial pneumonia (NSIP) [104], although a UIP pattern can be seen in up to 30% of cases [105]. A typical syndrome of CPFE can be observed in patients with SSc even in the absence of tobacco smoking [99, 106]. Emphysema is present in approximately 10% of SSc patients and is extensive in about one-quarter of them [107]. Exertional dyspnoea and decreased exercise tolerance are the most common complaints, and can be secondary to both ILD and PH. Older age, along with male sex, lower forced vital capacity, lower D_{LCO} and extent of disease on HRCT, is a predictor of mortality in SSc-ILD [108]. The prevalence of RHC-confirmed PH in patients with SSc ranges between 8% and 12% [84, 109] but it has been reported to be as high as 20% in patients at higher risk for this complication (*e.g.* those with disease duration >3 years, pulmonary fibrosis or D_{LCO} <60% predicted) [82]. The most frequent aetiology of PH in SSc is aberrant neoangiogenesis and pulmonary vasculopathy similar to idiopathic PAH (group 1 of the aetiological classification) but a variety of other mechanisms can contribute to its development, including left ventricular systolic and diastolic dysfunction (group 2); remodelling of the pulmonary veins with occlusive lesions resembling PVOD, and vascular chronic thromboembolism (group 3); and pulmonary fibrosis (group 4) [110].

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Sjögren's syndrome

Airway disease and ILD are frequent manifestations of pulmonary involvement in SS [111]. Lymphocytic infiltration of the upper airway mucosa may cause hoarseness and persistent dry cough. In addition, up to 20% of patients have recurrent bronchial and pulmonary infection [112]. Clinically significant ILD is rare, and in most cases SS-ILD follows a mild and self-limiting course, although a restrictive ventilator defect and reduced D_{LCO} are present in 17–37% of patients [113]. The most common histopathological patterns in SS-ILD are lymphocytic interstitial pneumonia (LIP) (characterised on HRCT by ground-glass opacities and thin-walled cysts in a peribronchovascular distribution) and NSIP [114]. Pulmonary lymphoma, which accounts for approximately 20% of all SS-associated lymphomas, and LIP have overlapping features. However, consolidation, large nodules and pleural effusions are more common in lymphoma, whereas cysts are more frequently seen in LIP [115].

Systemic lupus erythematosus

Up to 50% of patients with SLE develop some form of pleuropulmonary disease during the course of their disease, with pleuritis (with or without pleural effusion) representing the most common thoracic manifestation [116]. Compared to other CTDs, clinically significant ILD is relatively uncommon in SLE and is associated with longstanding (>10 years of duration) [117] and late-onset (>50 years of age) disease [118]. Similar to other CTDs, NSIP is the most common histopathological pattern, although LIP (particularly when secondary SS is present), organising pneumonia (OP), diffuse amyloidosis and UIP have also been reported [119]. On HRCT, NSIP is characterised by a combination of ground-glass opacity and reticular changes in a predominantly basal and peripheral distribution. However, the most common cause of pulmonary infiltrates in SLE patients is infection, which results from both the inherent disease-related immunological dysfunction and the use of aggressive immunosuppressive treatments [120]. As such, infection should be suspected in all SLE patients presenting with new/worsening respiratory symptoms or radiological abnormalities. Diffuse alveolar haemorrhage is a rare (it occurs in 1–5% of patients) but severe pulmonary manifestation of SLE, with a mortality rate of approximately 50% [121]. PH is a well-recognised complication and a common cause of death in patients with SLE [122]. Its prevalence in this setting is difficult to estimate, mostly due to the lack of a uniform definition of PH in earlier studies and the use of different diagnostic approaches, but it appears to be lower than that seen in SSc [123]. In addition, PH in the setting of SLE is a highly heterogeneous condition and may result from different pathogenetic mechanisms, including thromboembolic disease, immune-mediated vasculopathy and pulmonary vasculopathy similar to SSc-PH [124]. Overall, SLE-PH patients appear to be younger (mean±SE 45.5±11.9 *versus* 61.8±11.1 years) [125] and have a better prognosis than SSc-PH patients [77]. Other pulmonary manifestations of SLE include airway abnormalities (bronchiectasis and bronchial wall thickening) and diaphragmatic muscle weakness [126].

Polymyositis/dermatomyositis

Pulmonary involvement occurs in more than 50% of PM/DM patients, with ILD representing the most common and potentially the most devastating pulmonary complication of the disease [127]. As with most CTDs, ILD may be the presenting manifestation or be superimposed on established disease [128]. The so-called anti-synthetase syndrome (ASS), which is characterised by a combination of inflammatory myopathy, fever, inflammatory arthritis, Raynaud's phenomenon, "mechanic's hands", oesophageal dysmotility and carriage of an anti-transfer RNA synthetase antibody (*e.g.* anti-Jo-1, anti-PL-7 and anti-PL-12), confers a particularly high risk of developing ILD [129]. However, individuals who test positive for other types of myositis-specific antibodies, such as those directed at a macromolecular complex involved in RNA degradation and processing (anti-PM/Scl), display similar clinical manifestations, thus questioning the concept of ASS representing a unique clinical entity [130]. NSIP is the most common pattern seen on surgical lung biopsy, followed by UIP and OP [131]. Other pulmonary manifestations include respiratory muscle weakness due to active myositis, aspiration pneumonia (due to a combination of respiratory muscle weakness and pharynx and upper oesophagus muscle dysfunction) and, less commonly, PH or pleural disease [132].

Mixed connective tissue disease

Pleuropulmonary involvement is a common complication of MCTD [133] but it is often asymptomatic (and unrecognised) during the early phases of the disease [134]. Because MCTD is a clinical combination of SLE, SSc and PM/DM, pulmonary manifestations of any of these diseases may occur, including ILD, aspiration pneumonia, pulmonary vascular disease (*e.g.* haemorrhage, PH, thromboembolic disease and vasculitis), pleurisy (with or without effusion) and diaphragm dysfunction [135]. In a recent cross-sectional study of 126 Norwegian patients with MCTD, 52% had chest HRCT abnormalities, mostly lung fibrosis [136]. In addition, extensive disease (*e.g.* ground-glass opacity and reticular changes) was associated with a more severe restrictive ventilatory defect, lower exercise capacity and reduced survival.

Ankylosing spondylitis

Pulmonary involvement in AS consists most frequently of chest wall restriction (due to fusion of the costovertebral joint and ankylosis of the thoracic spine) and pleuroparenchymal abnormalities [137]. Upper lobe fibrobullous disease, a slowly progressive fibrosis of the upper lobes seen predominantly in men, with a male/female ratio of 50/1, is a common complication of AS, though clinically significant in less than 2% of patients [138]. Indeed, apical fibrosis is typically clinically silent unless extensive, or infected by bacteria or fungi. The mechanisms responsible for the apical fibrobullous changes are unknown. Less common pulmonary manifestations of AS include ILD, pleural thickening and effusion, and spontaneous pneumothorax [139]. A higher prevalence of obstructive sleep apnoea in patients with AS than that in the general population has also been reported. A combination of restrictive pulmonary disease, obstruction of the oropharyngeal airway due to temporomandibular joint involvement and compression of the medullary respiratory centres by cervical spinal joint arthritis are likely contributors to the development of this complication [140].

Table 7 summarises key clinical, physiological, radiological and histological features of CTD-ILD.

Pathophysiology

Ageing, CTD and lung fibrosis may share common pathogenetic pathways. Telomeres, the tandem repeats of the six-nucleotide unit sequence TTAGGG, represent a molecular cap of noncoding DNA that protects chromosome ends against degradation and fusion [141]. With cell division, telomeres tend to shorten, as the replication machinery does not copy fully to the ends. A specialised polymerase called telomerase, which has two essential core components, the reverse transcriptase (TERT) and the RNA template (TERC) [142], synthesises new repeats, thus extending the telomeres and preventing their shortening [143]. With repeated cell division, telomerase activity becomes insufficient to preserve chromosome length (with each cell division, telomeric repeats shorten by 30–200 base pairs), leading to cellular senescence and apoptosis [144].

Telomere shortening is a feature of normal ageing but it is more pronounced in disease characterised by accelerated ageing, such as cardiovascular disease, pulmonary fibrosis and diabetes [145]. CTDs are often associated with an inflammatory syndrome, increased leukocyte replication and defective telomerase activity, all contributing to telomere shortening [146]. Interestingly, haematopoietic progenitor cell telomeres from patients with RA are markedly shortened compared with age-matched controls, independently of disease duration, severity, activity and treatment [147, 148], suggesting that RA may be associated with intrinsic telomere shortening and progenitor cell dysfunction. However, telomere shortening can also be caused by systemic inflammation and autoantibodies, which are present years prior to RA onset. These two pathogenetic hypotheses are not mutually exclusive. In addition to age and telomerase function, several exposures contribute to accelerated telomere shortening *via* increased oxidative stress and systemic inflammation [145]. Cigarette smoking is one such exposure [149]. Indeed, long-term cigarette smoke exposure progressively depletes cells of their antioxidant and autophagic defences, reduces anti-ageing molecules, and impairs the DNA repair process and mitochondrial function, thereby driving cells towards apoptosis, senescence and stem cell exhaustion [150]. A dose–response relationship between cumulative lifetime exposure to tobacco smoking and telomere length has been reported [151], with 40 pack-years of smoking corresponding to 7.4 years of age-related telomere attrition [152]. Notably, telomeres are significantly longer in women than men after adjusting for age and smoking [153], but the reasons for this are not clear. Shorter telomeres and abnormalities in the telomerase components TERT and TERC have been found also in familial and occasionally sporadic cases of IPF, a chronic, progressive and almost invariably fatal disease of unknown origin [154, 155]. Age (*e.g.* the majority of patients are diagnosed after the age of 60 years), sex (*e.g.* the incidence is higher in males than in females with a nearly 2/1 ratio) and cigarette smoke are the strongest risk factors for IPF, with smokers presenting as much as a decade earlier than never-smokers [156].

Smoking: a unifying risk factor

Exposure to tobacco smoke has been associated with the development of several autoimmune diseases, including RA and SLE. In RA, smoking is thought to be caused by modifying self proteins, which are presented by certain alleles (so-called shared epitopes) with subsequent autoimmune attack and generation of anti-CCP antibodies [89, 157]. Indeed, anti-CCP antibodies are present several years before the first manifestations of the disease [158]. Tobacco smoking increases also the risk of developing ILD in RA patients [89, 157, 159]. Interestingly, the UIP pattern of lung fibrosis, which defines IPF, is also the most common pattern found in RA [160, 161], further emphasising the link between tobacco smoking and lung fibrosis. The relationship between the development of SLE and smoking is less clear. According to a very well supported hypothesis, tobacco exposure activates innate immunity and reduces the ability of macrophages to clear apoptotic cells, resulting in excess levels of exposed intracellular antigens, breakdown in tolerance and production of autoantibodies, such as those to dsDNA [162]. However, this hypothesis does not fully explain the association between smoking and SLE, as autoantibodies to dsDNA are not involved in

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TABLE 7 Clinical, physical, functional, radiological and histological features of connective tissue disease-associated interstitial lung disease (ILD)

	RA	SSc	SS	SLE	PM/DM	MCTD	AS
Clinical manifestations	Symptom onset around 50–60 years of age Men more likely to develop ILD than women Insidious development of exertional dyspnoea and dry cough Fever and chest pain less common	Fatigue Exertional dyspnoea Dry cough Chest pain uncommon	Onset of ILD is 5–10 years after the onset of SS More common in women Exertional dyspnoea and dry cough (often due to xerotrachea) Weight loss, fever and pleuritic chest pain can be present in patients with SS-associated LIP	More common in older patients and men Dry cough Dyspnoea Pleuritic chest pain Decreased exercise tolerance	Dyspnoea and dry cough Muscle weakness may influence severity of dyspnoea and risk of aspiration	More common in older patients Female preponderance Dry cough Dyspnoea Pleuritic chest pain	Male preponderance Often asymptomatic Cough Sputum Dyspnoea
Physical examination of the chest	Bibasilar crackles in up to 75% of patients Signs of PH and respiratory failure may develop in advanced disease Clubbing frequent in patients with the UIP pattern of RA-ILD	Bibasilar end-inspiratory crackles Clubbing uncommon Signs of cor pulmonale can be seen in advanced ILD or, more commonly, in SSc-PH	Bibasilar crackles in up to 60% of patients	Fever Cyanosis Bibasilar crackles Clubbing uncommon	Normal or dry bibasilar crackles Rapidly progressive dyspnoea and fever suggest infection	Dry bibasilar crackles Clubbing uncommon	Abnormal thoracic cage and anterior chest wall tenderness Clubbing does not occur
Pulmonary function tests	Restrictive ventilatory defect Reduced *D*LCO Oxygen desaturation during exercise	Restrictive ventilatory defect An isolated reduction in *D*LCO may be the first abnormality seen in SSc-ILD Oxygen desaturation on exercise is common both in SSc-ILD and SSc-PH	Restrictive ventilatory defect and reduced *D*LCO Small airway airflow obstruction common	Restrictive pattern Reduced *D*LCO Oxygen desaturation on exertion	Restrictive pattern Reduced *D*LCO Mildly decreased oxygen saturation on exertion Isolated restrictive pattern in patients with respiratory muscle weakness without ILD	Isolated reduction in *D*LCO in the early stages of ILD Restrictive pattern in more advanced disease	Restrictive ventilatory defect (largely due to reduced chest wall and spinal mobility)

Continued

TABLE 7 Continued

	RA	SSc	SS	SLE	PM/DM	MCTD	AS
Imaging findings on HRCT	Ground-glass opacity Reticular changes Traction bronchiectasis Honeycombing Linear opacities Consolidation	Ground-glass opacity in a peripheral distribution Bibasilar reticular changes Traction bronchiectasis Honeycombing rare Centrilobular nodules and fibrosis suggest recurrent aspiration	Ground-glass attenuation, centrilobular and subpleural nodules, linear opacities, interlobular septal thickening, bronchial thickening, bronchiectasis and thin-walled cysts (in patients with LIP and anti-SSB/La antibodies) Honeycombing is rare	Intralobular and interlobular septal thickening (predominantly in the lower lobes) Traction bronchiectasis Air-space consolidation Ground-glass attenuation Enlarged pulmonary arteries in cor pulmonale	Patchy ground-glass opacities Septal thickening Linear opacities Basilar consolidation Honeycombing	Septal thickening, ground glass opacities and linear opacities, all with peripheral/lower lobe predominance	Interlobular septal thickening Subpleural nodules Parenchymal bands Pleural thickening Apical fibrosis (usually bilateral)
Histological findings	UIP (predominantly) or NSIP pattern DAD and OP can be also seen Lymphoid aggregates Bronchiectasis Chronic bronchitis Follicular bronchiolitis	Fibrotic NSIP is the most common pattern but UIP may also be seen Pulmonary vascular changes consist mainly of concentric intimal thickening by fibromyxoid tissue and medial hypertrophy	NSIP (cellular, fibrotic or mixed) and LIP, which is characterised by a florid peribronchiolar and interstitial lymphoplasmacytic infiltration, are the most common histological patterns	NSIP is the most common histological pattern Diffuse alveolar haemorrhage and pulmonary vascular changes (chronic thromboembolic disease or vasculitis) can also be seen UIP, LIP and amyloidosis are rare	NSIP (either cellular or fibrotic) is the most common pattern of interstitial pneumonia OP, UIP and DAD can also be found Follicular bronchiolitis, LIP and vasculitis are rare	All histological features of PM/DM, SLE or SSc can be found; however, histological descriptions of chronic ILD in MCTD are scarce	Bronchiectasis Thin-walled bullae Fibrosis OP Vasculitis is typically absent

RA: rheumatoid arthritis; SSc: systemic sclerosis; SS: SS: Sjögren's syndrome; SLE: systemic lupus erythematosus; PM: polymyositis; DM: dermatomyositis; MCTD: mixed connective tissue disease; AS: ankylosing spondylitis; HRCT: high-resolution computed tomography; PH: pulmonary hypertension; UIP: usual interstitial pneumonia; D_{LCO}: diffusing capacity of the lung for carbon monoxide; NSIP: nonspecific interstitial pneumonia; DAD: diffuse alveolar damage; OP: organising pneumonia; LIP: lymphocytic interstitial pneumonia.

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all the clinical manifestations of the disease [163]. Moreover, contrary to RA, no study has convincingly addressed any gene–environment interaction between smoking and genes that confer susceptibility to SLE.

Tobacco smoking is the strongest risk factor for emphysema/chronic obstructive pulmonary disease (COPD) [164]. In addition, contrary to the traditional belief that PH in the setting of emphysema/COPD occurs secondary to hypoxia, it has recently been shown that the effects of tobacco smoke on pulmonary circulation (*e.g.* pulmonary vascular dysfunction and remodelling, and PH) precede alveolar destruction and emphysema [165–167]. In a hypothetical model of multiple "hits", host predisposing factors (*e.g.* short telomeres) may represent a first hit by lowering the threshold of lung damage that accumulates with age [145], with cigarette smoke representing a highly relevant environmental second hit as well as a critical determinant of the predominant phenotype (*e.g.* emphysema/COPD, cardiovascular disease, CTD, ILD/pulmonary fibrosis and PH). The need for multiple hits would also explain why these diseases tend to manifest late in life [168].

Treatment of CTD-ILD

Clinically significant (*e.g.* severe, extensive or progressive) CTD-ILD is commonly treated with immunomodulatory agents, although there is no consensus regarding which patients to treat, when and for how long. In addition, despite the variety of regimens used to treat CTD-ILD, the only large-scale, randomised controlled trials (RCTs) have evaluated the effectiveness of cyclophosphamide in patients with SSc-ILD [169, 170]. In this regard, the results of a currently ongoing clinical trial (www.clinicaltrials.gov identifier number NCT00883129) comparing the efficacy of a 2-year course of mycophenolate mofetil with a 1-year course of oral cyclophosphamide in patients with symptomatic SSc-ILD are eagerly awaited. The benefit of other immunomodulatory drugs (*e.g.* azathioprine, mycophenolate mofetil and tacrolimus) stem from case reports and observational case series [115]. Immunosuppressive treatments, however, are associated with significant adverse effects, including infection, a concern of particular relevance in elderly patients. Of note, the underlying CTD itself may contribute to increase the risk of infection [171]. Biological agents (*e.g.* tumour necrosis factor (TNF)-α antagonists), which are widely used in rheumatic diseases owing to their remarkable effectiveness, also appear to increase the risk of infection by opportunistic pathogens, including *Mycobacterium tuberculosis*, although the data in this regard are controversial [172, 173]. However, older age, along with pulmonary disease (*e.g.* COPD and asthma) and diabetes mellitus, has been consistently associated with the risk of bacterial infection requiring hospitalisation in RA patients treated with TNF-α antagonists [174–176]. Manifestations of the underlying CTD may mimic signs and symptoms of infection, making difficult a prompt diagnosis.

Treatment of CTD-associated PH

CTD-PH has a poor prognosis (poorer than idiopathic PAH) and once the diagnosis is confirmed by RHC, treatment should be considered. Current guidelines recommend that the same classes of PH drugs and treatment algorithm as in idiopathic PAH can also be applied to CTD-PH (table 8) [79]. This recommendation is based on the fact that patients with CTD (mainly SSc) have been included in most of the major RCTs of PAH therapy, including those of combination therapy. However, the magnitude of effect in the subset of patients with CTD-PH appears to be lower than in idiopathic PAH [79], probably because of the multifactorial and heterogeneous nature of PH in this setting (including potential involvement of the right ventricle and myocardium) and the difficulty in targeting simultaneously the multitude of pathways likely to be involved in the disease process. Moreover, agents that may be beneficial in idiopathic PAH, such as calcium channel blockers (in <10% of patients) or warfarin, generally have no role in CTD-PH [187–189].

Nonpulmonary comorbidities

Rheumatoid arthritis

On average, RA patients have 1.6 comorbidities and the number increases with the patient's age [190]. The excess mortality in patients with RA is largely attributable to cardiovascular disease (CVD), specifically ischaemic heart disease [191]. In addition, RA patients are at higher risk of atrial fibrillation [192] and heart failure, which tends to present with a different constellation of signs and symptoms than in non-RA individuals, and thus may be difficult to diagnose [193]. After CVD, cancer is the second most common cause of death in patients with RA [2, 194], with the increased risk being accounted for by a few specific malignancies (*e.g.* lymphoma, lung cancer and skin cancer) [194]. Moreover, RA appears to increase the risk of infection, particularly among individuals with more active and severe disease [171], although these patients are also more likely to receive corticosteroids and anti-TNF therapy [195, 196]. Increasing age is an additional strong predictor of infection [174]. Close surveillance of patients on immunomodulatory drugs (as well as immunisations appropriate for age and comorbid conditions) is critical in order to minimise morbidity and mortality from infection in patients with RA. Fractures resulting from osteoporosis, which is caused by limited physical activity and corticosteroid treatment as well as by the disease itself, rank highly among

TABLE 8 Pulmonary arterial hypertension (PAH)-specific therapies and their role in connective tissue disease (CTD)-associated PAH

Class of pulmonary vasodilators	Effect on CTD-PH/additional comments	Ref.
Compounds targeting the endothelin pathway		[177–179]
Endothelin receptor antagonists		
Bosentan	Bosentan improves 6MWD, WHO class and Borg dyspnoea score, and prolongs time to clinical worsening Bosentan is less effective in SSc-PH than in idiopathic PAH	
Ambrisentan	Ambrisentan improves 6MWD but the effect is larger in patients with idiopathic PAH	
Macitentan	Macitentan significantly reduces morbidity and mortality in patients with PAH	
Compounds targeting the prostacyclin pathway		[180–183]
Endothelin receptor antagonists		
Epoprostenol	Intravenous epoprostenol improves 6MWD and haemodynamics but has no effect on survival	
Treprostinil	Subcutaneous treprostinil improves cardiac index, pulmonary vascular resistance, dyspnoea-fatigue score and 6MWD	
Iloprost		
Selective oral prostacyclin IP receptor agonist		
Selexipag[#]	Selexipag significantly reduces the risk of a morbidity/mortality event in patients with PAH	
Phosphodiesterase-5 inhibitors		[184–186]
Sildenafil	Sildenafil treatment is associated with a modest improvement of 6MWD, functional class and haemodynamics	
Tadalafil	Tadalafil improves 6MWD and quality of life, and prolongs time to clinical worsening	
Soluble guanylate cyclase stimulators		
Riociguat	Riociguat treatment is associated with long-term improvements in exercise capacity	

PH: pulmonary hypertension; 6MWD: 6-min walk distance; WHO: World Health Organization; SSc: systemic sclerosis. [#]: no data on CTD-PH are currently available.

comorbidities in patients with RA, and contribute substantially to mortality, hospitalisation and disability [197, 198]. Long-term prognosis remains poor and the loss in life expectancy is approximately 7 years in female and 5 years in male patients [199]. Similarly, the direct costs of treatment and the indirect costs of disability and lost productivity are substantial [200].

Systemic sclerosis

Patients with SSc are at higher risk of developing several comorbid conditions. The overall comorbidity profile is similar to that observed in other autoimmune diseases [201] and this can be due to either toxicity of immunosuppressive therapies commonly used across autoimmune disorders or shared pathogenetic mechanisms. Data from two large US datasets showed that the risk of cardiovascular, renal and vascular diseases is higher among SSc patients compared to matched controls [202]. In the same study, SSc was also associated with a higher occurrence of liver disease, inflammatory bowel disease, multiple sclerosis and a number of neuropsychiatric disorders. SSc is associated with an increased risk of cancer, although the absolute risk is relatively low (standardised incidence ratio (SIR) 1.41). Men appear to have a higher risk of developing cancer than women (SIR 1.85) [203]. SSc substantially reduces life expectancy and men have a shorter life expectancy than women [204].

Sjögren's syndrome

The prevalence of several medical conditions, including cardiovascular, endocrine, gastrointestinal and psychological disorders, is higher in persons with primary SS than in the general population [205]. Patients with SS are also at increased risk of developing malignancy (relative risk (RR) 1.54), particularly non-Hodgkin lymphoma (NHL) (RR 13.76) [206], with those with persistent parotid gland enlargement being at particular risk [207]. The pathogenetic link between SS and NHL is unclear, but chronic antigenic activation of B-cells is believed to play a role [208]. Overall, patients with primary SS have slightly

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increased mortality rates compared with those of the general population and this is mainly accounted for by the excess lymphoproliferative disorders [209].

Systemic lupus erythematosus

At least one-third of SLE patients have one or more comorbidities, which are mostly related to disease activity and dose/duration of corticosteroid treatment [210]. CVD is a major cause of death in patients with SLE, and results mainly from atherosclerosis and thromboembolic events, although the prevalence of other "classical" cardiovascular risk factors, such as smoking (approximately 20% of SLE patients smoke), hypertension and dyslipidaemia, is also increased among patients with SLE [211]. Renal impairment, sustained inflammation and corticosteroid use (both directly and by inducing a metabolic syndrome) are additional contributors to premature atherosclerosis and hypertension [212]. The risk of heart attacks and strokes among SLE patients is 10 times higher than that of their age-matched controls, and SLE is considered an independent risk factor for CVD [213]. Other common complications include infections, an important cause of death in patients with SLE [214], and osteoporosis, which is caused by disease activity, limited mobility and corticosteroid use. Patients with SLE have also a several-fold increased susceptibility to certain types of cancer, particularly NHL, compared with the general population [215]. Patients with SLE have increased mortality and reduced life expectancy compared to the general population, with an overall 10-year survival rate of approximately 90% [216, 217].

Polymyositis/dermatomyositis

Patients with PM/DM are at higher risk of a number of comorbidities. Elderly patients have also an increased risk of developing malignancies, with substantially higher rates observed in DM [36]. The risk of malignancy may be particularly high in a subset of patients with DM who test positive for the myositis-specific autoantibody (anti-p155) directed against transcriptional intermediary factor 1γ [218]. Several recent studies have reported associations between PM/DM and hypertension, diabetes, ischaemic heart disease and venous thromboembolism [219, 220], suggesting that a comprehensive assessment of vascular risk factors is essential in these patients, particularly in the elderly. The higher risk of dying from cancer accounts for the almost three-fold higher mortality rates of patients with PM/DM compared to age- and sex-matched controls [221].

Mixed connective tissue disease

Similar to other CTDs, cardiovascular and thrombotic events are a major issue in MCTD (occurring in approximately 35% and 25% of patients, respectively), and remain, together with PH, a major cause of death in this patient population [222]. Mortality data in patients with MCTD are scanty, mainly reflecting the rarity of the disease. However, PH is a predictor of poor prognosis and the main contributor to the enhanced risk of premature death reported in these patients [223, 224].

Ankylosing spondylitis

Patients with AS are at increased risk for multiple comorbidities, including cardiovascular (*e.g.* hypertension), neurological (*e.g.* headaches), gastrointestinal (*e.g.* bowel and liver disease, and peptic ulcers), haematological (*e.g.* deficiency anaemia) and mental (*e.g.* depression and psychoses) disease [225]. In addition, AS patients have shorter life expectancy than the general population. Secondary amyloidosis, cardiovascular complications and fractures are the main contributors to the excess mortality observed in this patient population [226, 227].

Concluding remarks

CTDs represent an increasing burden on global health resources worldwide. Disease-related complications, long-term treatment-related adverse events and associated comorbidities are major contributors to the significant mortality and morbidity associated with these conditions. ILD has long been recognised as a complication of CTD but its potential for morbidity, mortality and reduced life expectancy has only recently been fully appreciated. CTDs in elderly patients pose a number of diagnostic and therapeutic challenges. In fact, because they typically affect young to middle-aged patients, the diagnosis of late-onset CTD is often delayed, mainly by virtue of atypical presenting manifestations in this age group, and often established only after extensive investigation. In addition, the accuracy of rheumatological laboratory tests may differ in older compared to younger patients (with decreased specificity of ANA), thus limiting the diagnostic value of this test in elderly patients [228, 229]. Treatment decision-making is similarly difficult. In fact, while in principle, therapeutic strategies should not differ substantially from that recommended in younger patients, treatment of elderly patients is often complicated by comorbidities, increased rate of treatment-related adverse events and polymedication.

The number of elderly people with CTD and CTD-related lung disease is growing considerably. Yet, due to the lack of specifically designed evidence-based guidelines for management, this patient subgroup is often either undertreated (by virtue of its inherent frailty) or inadequately managed despite the availability of effective and well-tolerated drugs. Clinical trials focusing on elderly patients with CTD and CTD-associated lung disease are therefore urgently needed.

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