# Pulmonary Complications of Rheumatoid Arthritis

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## Abstract

Rheumatoid arthritis (RA) is a common chronic autoimmune disorder that characteristically causes joint inflammation and damage. In addition, many patients develop extraarticular manifestations which may cause significant comorbidity and premature mortality.

Some respiratory tract involvement of the upper and lower airways and parenchymal disease features are unique to RA, including cricoarytenoid arthritis and RA pulmonary nodulosis, and others, especially the interstitial parenchymal involvement, occur in many other idiopathic and autoimmune diseases. The pathophysiology of lung disease is not well understood. Rheumatoid lung disease may even predate the onset of joint disease, and could be triggered by chronic airway and alveolar epithelial injury. Chronic systemic inflammation and risk factors such as cigarette smoking, infection, host genetics, and immune dysregulation are contributors. Treatment of the respiratory disease is directed at reducing the systemic inflammation of RA. Less well understood is the management of the interstitial lung disease of RA, for which antifibrotic and immune suppressive agents may be helpful. The management of RA-related lung disease is perhaps the major remaining hurdle in reduction of the disease burden related to extraarticular manifestations of this disease.

**Keywords**
- rheumatoid arthritis
- airways disease
- lung disease
- interstitial lung disease
- pathology
- diagnosis
- treatment



Rheumatoid arthritis (RA) is the most common autoimmune-mediated joint disease, affecting about one percent of the population of the United States and Europe. While a disease of joints, it is best understood as a systemic disorder which can affect multiple organs, including the respiratory tract. Severe extraarticular manifestations such as vasculitis, Felty's syndrome, glomerulonephritis, pericarditis, pleuritis, scleritis, and interstitial lung disease (ILD) develop in a variable number of patients, causing major morbidity and premature death in those who develop them. The manifold respiratory tract features of RA are summarized in ►**Table 1**.

Perhaps attributable to improved treatment of RA in recent decades, it is thought that the incidence of most of these manifestations is decreasing, with the exception of ILD, the pathobiology of which is poorly understood and which remains a difficult management problem.[1–3] Although progression is slow in most cases, in aggregate, diagnosis of symptomatic ILD in patients with RA is associated with an up to threefold increase in premature mortality compared with RA patients without ILD.[2] The aim of this review is to synthesize the current evidence regarding the presentation and management of the pulmonary complications of RA, with particular attention given to ILD.

* Both the authors contributed equally to this work.

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**Table 1** Pulmonary features of rheumatoid arthritis

| |
|---|
| Pleural disease |
| Rheumatoid nodulosis |
| Airways disease |
| Parenchymal disease |
| Usual interstitial pneumonia (UIP) |
| Nonspecific interstitial pneumonia (NSIP) |
| Organizing pneumonia (OP) |
| Lymphocytic interstitial pneumonia (LIP) |
| Desquamative interstitial pneumonia (DIP) |
| Acute interstitial pneumonia (AIP) |
| Diffuse alveolar hemorrhage (DAD) |
| Other diseases of thorax and lung in rheumatoid arthritis |
| Apical fibrobullous disease |
| Thoracic cage immobility |
| Venous thromboembolic disease |
| Pulmonary hypertension |
| Vasculitis |
| Other complications affecting the lung in patients with rheumatoid arthritis |
| Pulmonary toxicity of drugs used to treat rheumatoid arthritis |
| Lung cancer |
| Lung infections |

## Rheumatoid Arthritis-Related Interstitial Lung Disease

### Epidemiology

#### Frequency

The frequency of RA-related ILD (RA-ILD) reported in the literature is variable due to differences in how it is defined, study design, and the populations analyzed.

#### Prevalence

Cross-sectional analyses of patients with RA consistently report a high prevalence of abnormalities consistent with ILD on radiology, and/or pulmonary function testing, ranging between 15 and 58%.[4–10] Symptomatic disease is less common than subclinical disease. For example one group of authors found a prevalence of clinically significant disease of 14% compared with 44% who had abnormal investigations but no symptoms.[5] Another group found that 6.8% of women and 9.8% of men with RA had ILD listed as a factor contributing to death on their death certificate.[3] A Japanese study group performed high-resolution computed tomography (HRCT) on patients following their first visit to a specialist rheumatology clinic and found a prevalence of ILD changes of 6.7%.[11] An insurance database study using International Classification of Diseases (ICD) codes identified an outpatient prevalence of lung disease (comprising ILD and pleurisy) of 0.56% in 1997, increasing to 0.98% by 2006, likely reflecting increasing diagnostic sensitivity and increasing use of CT scanning.[12] Inpatient prevalence ranged from 2 to 4% in the 1980s to 3.86% in 2006.[12]

The most common radiological pattern of RA-ILD in the Western world is usual interstitial pneumonia (UIP), which is also observed in other types of ILD such as idiopathic pulmonary fibrosis (IPF), asbestos-related fibrotic lung disease, some drug induced-ILDs, and chronic hypersensitivity pneumonitis.[13] Radiologic and histopathologic reports cite a relative frequency of approximately 60% of RA-ILD cases as UIP, but estimates are strongly influenced by detection modalities and definition.[14–17] For example, using strict IPF diagnostic criteria, one study of 157 patients with RA-ILD detected a definite UIP pattern in 24% of cases on CT.[17] Using a broader definition, ignoring disease distribution and the presence of a mosaic attenuation pattern, 35% were classified as having a definite UIP pattern.[17]

The other common HRCT presentation in RA-ILD is a nonspecific interstitial pneumonia (NSIP pattern) in approximately 20% of cases of RA-ILD.[14–16] The relative frequency of UIP and NSIP varies somewhat according to detection and diagnostic approach, and environmental or genetic factors may influence phenotype. For example, NSIP was found to be more common than UIP in a large cohort of patients with RA-ILD from China.[18] Other patterns of parenchymal lung disease occurring in patients with RA include organizing pneumonia (OP), desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia (LIP), diffuse alveolar damage (DAD), and acute interstitial pneumonia (AIP; ►**Table 1**).[13,19]

#### Incidence

Incidence data for ILD in RA focus on NSIP and UIP. There are no population-based or substantial cohort studies of incidence or frequency of OP, DIP, LIP, DAD, or AIP. A population-based cohort study reported the lifetime incidence of RA-ILD defined by a combination of clinical, radiological, and pathological criteria in Rochester, United States, as 7.7% for patients with RA, and 0.9% for non-RA subjects (hazard ratio [HR]: 8.96; 95% confidence interval [CI]: 4.02–19.94).[2] Another cohort analysis from the same locality found a 10-year incidence of pulmonary fibrosis of 5% for patients with RA diagnosed between 1995 and 2007, not significantly different from a cohort diagnosed between 1985 and 1994.[1]

Patients enrolled in the Institute of Rheumatology Rheumatoid Arthritis (IORRA) cohort in Japan, followed for a period of 2.5 years from 2004 to 2006, had an age-adjusted incidence of RA associated interstitial pneumonia (defined by an HRCT pattern of NSIP or DAD) of 1.056/1,000 patients for the total patient population, 0.6770/1,000 for women, and 1.452/1,000 for men.[20] A cohort of patients with RA from England found an annualized incidence of 4.1/1,000, and 15-year cumulative incidence was 62.9/1,000. Half developed it either at baseline or within 3 years of onset of RA.[21]

#### Risk Factors

*Patient-related factors*: Demographic factors associated with RA-ILD include male sex and older age.[2,5,7,21–25] HLA-DRB1*502 has also been associated with RA-ILD.[11] Few authors have looked at the effect of ethnicity on the development of

RA-ILD, and making inferences from studies performed on homogeneous groups from different parts of the globe is problematic. One group of authors found Hispanic patients were more likely to develop extraarticular manifestations of RA than Asian patients (odds ratio [OR]: 2.53; 95% CI: 1.26–5.09), in a population where the prevalence of RA-ILD was 3.6% overall.[25]

*Disease-related factors*: Reported disease-related factors include disease duration, radiographic joint damage, and seropositivity for rheumatoid factor and anticitrullinated protein antibody (ACPA), usually measured as anticyclic citrullinated peptide antibody (anti-CCP).[2,8,10–12,23,25]

*Environmental factors*: Smoking has been associated with the development of RA itself, and also increases the risk for developing RA-ILD with a dose–effect relationship.[7,12,22–24,26,27] Smoking may also induce UIP, which may also occur in nonsmokers.[28] Other environmental exposures have not been specifically studied in relation to the development of RA-ILD; however, various occupational exposures to dust, fumes, and metal inhalations may increase the risk of developing RA.[26] Specific agents that have been implicated include silica, asbestos, mineral oils, pesticides, electronics work, textiles, and roadside dust.[26]

## Pathobiology of Rheumatoid Arthritis Lung Disease

The pathobiologic mechanisms of lung disease in RA are incompletely understood. Putative and proven triggers of lung disease in these patients include infections, host genetics, smoking, mucosal injury and disease, epigenetic factors, and abnormal immune cell function including premature senescence. Because the pathobiology of parenchymal disease is perhaps the least well understood and most clinically challenging of the respiratory manifestations, this review focuses on RA-ILD.

It is likely that lung injury is initiated by chronic airway and epithelial injury, which creates conditions in the susceptible host for the development of autoimmunity, in many cases possibly ahead of the systemic and characteristic joint manifestations of the disease. This has led to the concept that the lung may be "ground zero" for RA disease genesis.[29] Subsequent chronic inflammation leads to airway and lung parenchymal remodeling and fibrosis with their associated morbidity.

The lung disease of RA is not due to a specific infectious cause, but dysbiotic triggers in mucosal sites of the mouth and airways appear to play a role in creating the conditions for expression of the systemic disease. One result is the generation of ACPA at synovial, rheumatoid nodule, pulmonary, and other sites, often many years before synovitis becomes clinically apparent.[30]

Supporting this idea is the fact that immunoglobulin A (IgA) isotype ACPAs have been identified in individuals at risk of RA, which is of particular interest because of the roles IgA antibodies play in regulating mucosal defenses.[31] Further, ACPA may be found in both seronegative and seropositive patients with RA, and indeed, ACPA may be present in the sputum, but not in serum, in some individuals at risk of future RA, supporting the idea that ACPAs are first generated in the lung.[31] Levels of ACPA autoantibodies have been reported to be higher in the bronchoalveolar lavage (BAL) than serum of patients with RA, underlying the primacy of the lung as the possible site of initial autoimmune activation resulting in RA. These autoantibodies have been associated with bronchiectasis even in patients without RA, and represent a general immune response, possibly resulting from molecular mimicry.[32]

These environmental exposures in the airways and other mucosal sites lead to breakdown of tolerance to autoantigens, leading to T-cell activation targeting self-peptides. This breakdown of tolerance may be particularly hastened by cigarette smoke exposure, particularly in the context of various HLA-DRB-related genes, facilitating the generation of citrullinated proteins including vimentin, which are associated with seropositive but not seronegative disease.[33]

Mediators of cigarette smoking-induced lung disease include dendritic cells (DCs). Cigarette smoke impairs the generation of tolerance to certain exogenous antigens and suppresses tolerogenic DCs.[34,35] In this context, local lung epithelial DC function is suppressed by transforming growth factor-β (TGFβ), promoting immune tolerance, while others such as granulocyte macrophage colony stimulating factor (GM-CSF) promote DC-mediated inflammation and autoimmunity.[35–37]

Exactly how tobacco smoke may induce autoimmunity is not clear. It is composed of many chemicals, of which polycyclic aromatic hydrocarbons (PAHs) are known to activate the aryl hydrocarbon receptor, which is upregulated in RA synovial tissues.[38] Mice that are aryl hydrocarbon receptor deficient are resistant to collagen-induced arthritis and have attenuated Th17 immunity.[37] Peptidylarginine deiminase (PAD) enzymes regulate the conversion of peptidylarginine to peptidylcitrulline in a calcium-dependent reaction referred to as citrullination. PAD2 levels in the upper and lower airways are elevated in smokers, who also have higher levels of citrullinated peptides in BAL cells.[39]

Another tobacco smoke component implicated in immune dysregulation is nicotine. In a dose-dependent relationship, nicotine induces neutrophil extracellular trap (NET) formation, which is further enhanced in the presence of ACPAs.[40] NET formation requires histone citrullination by PAD4, which is itself induced by cigarette smoke (at least in a murine model of collagen-induced arthritis exposed to cigarette smoke), a process which is at least initiated in the airway mucosa.[40]

In recent years, it has become appreciated that dysregulation of the microbiome in the mouth, lungs, and gut through smoking, antibiotics, and other exposures contributes in some way to a predisposition toward autoimmunity.[29,41] While there is cross-talk between the microbiomes of these mucosal surfaces, most studies in RA have focused on the gut–joint axis rather than the lung–joint axis. At least one study addressing this relationship reported lower microbe diversity in the BAL fluid from untreated patients with RA than in non-RA comparator subjects.[42]

Studies of dysbiosis in RA thus far do not provide a straightforward explanation of the role of various bacteria in immune dysregulation. Some investigators report a lower abundance of *Actinomyces* and *Burkholderia* and increased

abundance of *Pseudonocardia,* the latter of which is associated with increased disease activity in RA.[43] *Porphyromonas gingivalis* has been linked to periodontitis in smokers and patients with RA, but at the same time, there may be lower abundance of this bacterium in BAL of patients as compared with healthy controls.[43,44] In RA, there appears to be a link between RA-associated HLA molecules and citrullination and *P. gingivalis* which may be promoted by smoking.[45,46]

The directionality of citrullinated peptides like ACPA as a cause of lung disease (the lung as a target of ACPA) in patients with RA, or as causational for the joint disease (e.g., the lung as "ground zero" for RA), is as yet not fully clarified. Existing evidence supports the role of chronic airway disease and lung injury and dysbiosis as inducers of ACPA generation and inflammation. This directionality is supported clinically by observations that higher ACPA levels correlate with reduced diffusion capacity for carbon monoxide (DLCO) characteristic of ILD.[46] ACPAs cause local mucosal airway and interstitial lung tissue injury in several possible ways. These include formation of immune complexes, promotion of inflammatory cytokines such as interleukin (IL)-6, IL-8, and tumor necrosis factor α (TNFα) and NET formation.[47,48]

Several other intrinsic host genetic and epigenetic factors are important in the development of RA-ILD. Senescent fibroblasts secrete a variety of cytokines, chemokines, matrix remodeling proteases, and growth factors which may promote tissue remodeling and fibrosis.[49] Premature senescence may have a direct role in the development of lung remodeling and fibrosis.[50] Single nucleotide polymorphisms in the promoter of the oligomeric mucus/gel-forming gene 5B (MUC5B) appears to predispose to interstitial fibrosis and risk for development of IPF and RA-ILD, but not for increased risk of pulmonary fibrosis in myositis or scleroderma.[51–55] This MUC5B promoter polymorphism is more prevalent in patients with RA who have ILD when compared with patients with RA who do not have lung disease.[55] The role of epigenetic mechanisms such as hypo- and hypermethylation in promoting lung disease in RA has not been well investigated.

Other factors that may promote RA-associated lung fibrosis include dysregulation of TGFβ1 as a key regulator of epithelial–mesenchymal transition, fibroblast proliferation and accumulation of extracellular matrix, and generation of Th17 cells and overexpression of IL-17A.[56,57] Several other proteins such as matrix metalloproteinases, Krebs von den Lungen 6 (KL-6), surfactant proteins, chemokines, procoagulant factors, and others have been identified as relevant to development of IPF, but their role in RA-ILD is thus far uncertain.[58]

## Clinical Presentation and Evaluation of RA-ILD

### Interstitial Lung Abnormality

Interstitial lung abnormalities (ILAs) are defined as specific patterns of increased lung density on CT scans in patients with no prior history of ILD. As a referent, four large prospective cohort studies which analyzed general population or research participants found that ILAs were present in up to 10% of subjects and are associated with increased all-cause mortality compared with subjects without ILA, independent of age and smoking status.[59]

Subclinical ILAs are reportedly detected in up to half of patients with RA.[60] In general, the natural history of ILAs in patients with RA is poorly characterized and optimum surveillance/management is unclear, but certainly the finding of fibrotic ILA even in the absence of symptoms should prompt periodic longitudinal follow-up. The clinical presentation and evaluation of RA-related ILA is similar to that of other forms of ILD and is briefly reviewed below. The histology of RA-related ILAs is not pathognomonic of RA; the classification and histologic patterns of the various forms of interstitial pneumonias are reviewed elsewhere.[60]

A combination of ILD patterns can be found in the same individuals during one snapshot CT scan or over their disease course.[19,61] In addition, it is often difficult to tease out the cause of clinical symptoms in patients presenting with RA-ILD, which may be due to acute exacerbation of ILD, previously undiagnosed with superimposed infection, drug induced, or related to occupational and environmental precipitants.

ILD can predate the development of inflammatory arthritis or RA serology and usually evades diagnosis unless the radiology or pathology is particularly suggestive of underlying RA disease.[2,18,62] In a Danish cohort, 14% of patients presented with ILD at least 1 to 5 years prior to their RA diagnosis.[62] This observation highlights the importance of longitudinal multidisciplinary team review of patients diagnosed with IPF.

### Clinical Presentation of RA- ILD

A persistent dry cough, progressive exertional dyspnea, and fatigue are the main presenting symptoms in patients with ILD, regardless of underlying cause. In patients with RA, the symptom of exertional dyspnea is often masked by their limited exercise capacity related to joint disease and dry cough attributed to airways disease or gastro-oesophageal reflux disease leading to diagnostic delay.[2,61]

In early RA-ILD, the patient may have no demonstrable respiratory or cardiovascular signs at rest and normal resting oxygen saturations and respiratory rate. However, with progressive and usually advanced fibrotic lung disease there is evidence of reduced lung expansion, tachypnea, bibasal "velcro-sounding" crackles, and there may be signs of cor pulmonale. A blinded prospective study reported that the clinical sign of "velcro-sounding" crackles on auscultation in patients without a prior diagnosis of ILD correlated with fibrotic ILD (FILD) on subsequent HRCT.[63] Of subjects with bilateral "velcro-sounding" crackles, 81% had FILD, whereas only 26.8% of subjects with unilateral crackles had FILD. Importantly, the absence of "velcro-sounding" crackles was not completely reassuring as 19.7% of such subjects had evidence of FILD on subsequent HRCT.[63]

Digital clubbing is another clinical marker of adverse prognosis and in RA-ILD. It is usually associated with a UIP pattern and occasionally may be found in other types of RA-ILD. There may also be signs of pulmonary hypertension and resulting right heart failure either related to the lung fibrosis or less commonly pulmonary arterial hypertension associated with RA.[60,64]

### Evaluation of Patients with RA-ILD

Patients with RA should have lung function tests and a chest radiograph at initial diagnosis of RA, particularly if there is a smoking history. To this point, the long-term clinical impact of this approach has not been systematically evaluated. Especially in the symptomatic patient, other studies useful in the clinic as well as in clinical trials in RA-ILD may include HRCT, 6-minute walk time (6MWT), pulmonary function studies with DLCO, an index of breathlessness such as the Borg scale, global assessment, BAL, and with decreasing frequency lung biopsy.[65,66]

### High-Resolution Computed Tomography

HRCT is currently the standard for assessing the pattern of ILD in RA, and can provide clues about the extent of disease and associated pathologies. A clinical challenge has been to predict which patients will develop progressive fibrosis. In contrast to IPF, the distribution of disease in RA-ILD may not be basal-predominant, as honeycomb cysts and reticulation may be concentrated peripherally in the middle or upper zones of the lungs.[67] Jacob et al have published a predictive model using HRCT demonstrating that approximately 23% of patients with RA-ILD will develop IPF-like progressive fibrosis, emphasizing that the presence of honeycombing in RA-ILD, rather than its location, best determines patient outcome.[17] Overall, survival of patients with honeycombing occurring in an IPF-like distribution was 53% at 3 and 6 years.[17] In the clinic, the indications and timing of HRCT evaluation are not standardized; it is the authors' practice to obtain HRCT in symptomatic patients, and in follow-up dictated by clinical symptoms.

### Pulmonary Function Tests

The majority of patients with RA-ILD will have restrictive physiology even when asymptomatic.[13] Ideally baseline pulmonary function tests should be performed in every patient with RA (particularly ever-smokers) at presentation regardless of respiratory symptoms. Recommended investigations include spirometry, lung volumes, and an assessment of gas exchange since restrictive abnormalities in RA can be due to musculoskeletal pain/weakness or pleural abnormality, while a reduction in gas exchange (DLCO) of $<80\%$ is sensitive for predicting presence of ILD and, together with extent of fibrosis on HRCT, is best at predicting outcome.[5,28,68,69]

Clinically meaningful changes in pulmonary physiology include a forced vital capacity (FVC) $\leq 10\%$ and DLCO $\leq 15\%$, similar to patients with IPF, whereas treatment response of stable lung function rather than decline is often what is hoped for.[65] Even in the absence of symptoms, pulmonary function tests may reveal a restrictive ventilator defect with decreased gas diffusion capacity of the lung for carbon monoxide (DLCO).

### Bronchoalveolar Lavage

The main utility of BAL in RA-ILD is in excluding opportunistic infection and other conditions such as malignancy or eosinophilic disease when patients present with ground glass abnormality superimposed on established fibrotic lung disease. There is little evidence that BAL findings such as lymphocytosis are useful markers of the underlying RA-related inflammatory disease for guiding the timing of immunomodulatory therapy.

## Management and Prognosis of RA-ILD

The mortality impact of symptomatic RA-ILD is profound; the risk of premature death is about threefold higher than that of patients with RA who do not have lung disease.[70] Survivorship reports from most studies are in line with a result from a study of patients with RA-ILD (108 patients with UIP and 29 with NSIP) on HRCT, reporting that those with RA-UIP had a shorter survival time than those with RA-NSIP (log rank $p = 0.02$). In that study, lower baseline % predicted FVC (FVC% pred.) (HR: 1.46; $p < 0.0001$) and a 10% decline in FVC% pred. from baseline to any time during follow-up (HR: 2.57; $p < 0.0001$) were independently associated with an increased risk of death.[28] Patients with RA-ILD with progressive fibrosis as seen in IPF on HRCT have the worst prognosis; the 4-year mortality is equivalent to that of IPF.[17] In the study of Jacob et al, functional indices were less predictive of outcome at baseline, and positive smoking history did not predict outcome.[17] In the current review, treatment focus is on the UIP–NSIP spectrum of disease. In general, treatment with immunomodulatory therapy is considered in patients with clinical, functional, or radiological deterioration and radiological and pathological patterns other than UIP.

Patients with rapidly progressive disease, especially those with OP, LIP, and NSIP, may respond to glucocorticoid therapy as suggested by society guidelines, generally at initial prednisone equivalent doses of 0.5 mg/kg body weight, tapering over months.[71] In RA-ILD of NSIP type, rituximab, mycophenolate mofetil, cyclophosphamide, abatacept, and azathioprine have all been employed, although little guidance is provided regarding specific dosing regimens or treatment duration.[61,64,70–75] The indications for immunomodulatory therapy of NSIP have been suggested as younger age ($<70$ years of age), progressive symptoms and marked decline in FVC and DLCO over less than 1 year, and worsening disease on HRCT, although there are no agreed upon parameters for these measures.

A useful referent for UIP is the Panther Study, which was a randomized control trial of immunomodulatory therapy including prednisone and azathioprine versus placebo in patients with a clinical diagnosis of IPF (UIP pattern on HRCT but no underlying RA, connective tissue disease, drug exposures, environmental or occupational exposures).[76] This study demonstrated that treatment with immunomodulatory therapy reduced survival in those patients.

To date, there are no adequately powered randomized clinical trials in RA-ILD to provide guidance in the management of the symptomatic patient. A retrospective study of RA-related fibrotic lung disease of UIP pattern showed that using glucocorticoid therapy alone or in combination with immunomodulatory therapy appeared to stabilize the fibrotic lung disease in half of the patients receiving treatment.[77] Patients receiving treatment appeared to have a similar outcome to RA-ILD patients with UIP pattern not receiving

treatment but may have had more severe disease at the outset of therapy.[77]

Based upon current evidence and experience, it is unlikely that patients with RA and incidental finding of fibrotic lung disease of UIP pattern on HRCT without evidence of progression radiologically or on respiratory physiology will benefit from immunomodulatory therapy. In most patients, decline in parameters of lung physiology, especially DLCO and FVC, is slow,[78] and there is no evidence that commencing immunomodulatory therapy in subclinical RA-ILD stabilizes the disease or prevents progressive decline in radiology, physiology, and symptoms. When there is doubt about the nature of the underlying parenchymal disease on HRCT and aggressive immunosuppressive therapy is being considered, surgical lung biopsy may be useful to distinguish between UIP and NSIP, as NSIP may be more responsive to therapy. The mortality and morbidity related to lung biopsy is significant and patient advocacy is required.[61,64,73,74]

Immunomodulatory treatment targeting the joint disease should be pursued in all patients, and all patients should be offered preventative vaccination.[19,61] When there is subclinical ILD, targeted treatment of active joint disease in RA takes priority with disease-modifying drugs (with the potential to cause or exacerbate parenchymal lung disease) and should be monitored with serial lung function tests, chest radiographs, and 6MWT three to six monthly alongside the immunomodulatory therapy to assess ILD response and ensure no adverse effects in the lung.[79] If there is improvement or stability, then monitoring could be deferred to yearly. Unfortunately, there is no clear choice of immunomodulatory agent beneficial for treating both RA joint disease and ILD.

Antifibrotic medication may slow the relentless progressive fibrosis in patients with IPF.[80,81] Unfortunately this treatment does not generally improve symptoms or halt or reverse disease in real-world patients and side effects of therapy are not insignificant. There is insufficient evidence to support its use thus far in RA-ILD, although it may ultimately be a promising approach. The similarity in disease expression and pathogenetic mechanisms between the progressive fibrotic form of RA-ILD and IPF argues for a similar therapeutic approach, and for not excluding this subgroup of patients with RA-ILD from treatments and clinical trials of approaches used in IPF.[82] Currently, a phase II, randomized, double blind, placebo controlled trial of pirfenidone for the treatment of RA-associated interstitial lung disease (TRAIL-1) is underway to address this question.[83]

Optimizing the quality of life in patients with RA-ILD is a vital aspect of disease management.[75] A high symptom burden of dyspnea and pain has been reported in the last year of life of patients suffering from RA, including RA-ILD.[84] In the study by Cho et al, palliative care referral was infrequent (15%), and patients died on average within 8 days of referral.[84] Integrated respiratory, rheumatology, and palliative care is required to improve quality of life and outcomes for patients with RA-ILD. Nonpharmacological interventions such as fatigue and breathlessness courses and hand-held fans among others complement pharmacological strategies with morphine and occasionally benzodiazepines to lessen the suffering of patients with advanced lung disease and in particular ILD.[85–87]

In severe or rapidly progressive RA-ILD, lung transplantation should be considered in patients without significant contraindications or comorbidity. Retrospective analysis from transplant centers demonstrate that the 1-year survival following transplant is comparable with that in other fibrotic lung diseases such as IPF and although numbers are small, patients with RA report a significant improvement in quality of life related to improved respiratory symptoms.[88,89]

## Other Diseases of Thorax and Lung in Rheumatoid Arthritis

### Pleural Disease

#### Frequency

Pleural effusions are common in RA, however the majority of cases are either asymptomatic or are not clinically significant. Radiographic sequelae of pleurisy were found in 24% of men and 16% of women with RA in one study,[90] and pleural effusions have been found in over half of patients in autopsy studies.[91] In contrast, pleural effusions have been found in 3 to 5% of patients in older studies based upon predominantly clinical assessment.[92,93] The annual incidence of rheumatoid pleural effusion in RA populations has been reported as 0.34% in women, and 1.54% in men.[94] Symptoms consistent with pleuritic disease are commonly reported, in approximately 20% of patients.[93] Risk factors include male sex, high rheumatoid factor, and presence of subcutaneous nodules.[92–96] HLA B8 and Dw3 have been associated with rheumatoid pleural effusion.[96]

#### Clinical Presentation

Patients with rheumatoid pleural effusion may present with dyspnoea, pleuritic chest pain, and fever. In general, pleural effusions develop in the context of established joint disease; however, pleural effusions can develop concurrently with joint disease, prior to, or in the absence of clinically apparent joint disease.[93,97] Frequently, there is no correlation between the appearance of a rheumatoid pleural effusion and joint disease activity.[98]

#### Pathologic Findings

Macroscopically, a granular appearance of the parietal pleura can be seen on thoracoscopy.[99] Cytology of rheumatoid pleural effusions characteristically shows spindle cells of histiocytic origin, multinucleated giant cells, and necrotic background debris.[100] Pleural biopsy histology shows replacement of normal mesothelial cell covering with a pseudostratified layer of epithelioid cells, which focally form multinucleated giant cells, and chronic stromal inflammation with small papillae containing branching capillaries; however, changes may be nonspecific.[99,101]

#### Complications

The prognosis is generally good. The mean time to resolution of rheumatoid pleural effusion was 14 months in one study.[99] In another series, 13/19 resolved within 3 months, but the

remaining patients had a more protracted course, and 4/19 had persistent effusion at time of death.[93] Long-standing pleuritis can lead to loculation, pleural thickening, and fibrosis, and eventually trapped lung.[102]

Empyema may complicate rheumatoid pleural effusions due to immune dysfunction related to RA itself, immunosuppressive therapies, increased frequency of chronic suppurative lung diseases including bronchiectasis, and the formation of bronchopleural fistulae caused by the rupture of subpleural pulmonary nodules.[103]

### Evaluation

Pleural fluid analysis in RA reveals an exudate that classically has low glucose, low pH (<7.30), elevated protein, high lactate dehydrogenase activity, lipids and cholesterol, and rheumatoid factor.[101] Glucose and pH levels may be normal in acute or recent disease, and can become lower with increasing duration of effusion.[104] pH levels in rheumatoid pleural effusions are generally not as low as those seen in empyema.[103] Most commonly lymphocytes predominate; however, neutrophilic and eosinophilic effusions are also seen.[101] A pseudochylothorax can occur, characterized by high cholesterol content and milky-appearing pleural fluid. The pathogenesis of pseudochylothorax is unknown. The elevated cholesterol has been considered to be due to accumulation of break-down products of red and white blood cells in the context of long-standing inflammation, although the finding that some patients presenting with pseudochylothorax have a short duration of pleural disease challenges this notion and suggests that perhaps a more acute process leads to the active accumulation of cholesterol.[105]

### Management

Optimal management of pleural disease has not been comprehensively studied. Small asymptomatic effusions do not require specific therapy. Whether or not larger effusions need treatment to prevent complications such as trapped lung is controversial.[95] Oral glucocorticoids have been used with success.[93,101] Intrapleural glucocorticoids have also been used successfully, but others have reported lack of resolution or reaccumulation despite intrapleural glucocorticoids.[93,95,98,106] Successful treatment with abatacept has been reported, as well as tocilizumab.[107,108]

Chest drain insertion can be considered for symptomatic effusions. For recurrent and or large symptomatic effusions, pleurodesis may be considered, and decortication may be required, although the optimal indications have not been established.[95] Indwelling pleural catheters have been shown to be effective in the management of refractory benign pleural effusions, but there is little evidence to make recommendations on their use specifically for rheumatoid pleural effusions.[109]

## Rheumatoid Nodulosis and Pneumoconiosis (Caplan's Syndrome)

### Frequency

Cross-sectional studies of RA patients undergoing HRCT report pulmonary nodules in 4 to 28% of patients.[15,110] Caplan's syndrome, also known as rheumatoid pneumoconiosis and originally described in Welsh coal miners, is characterized by multiple pulmonary nodules which may coalesce. It occurs in patients with RA exposed to inorganic dusts including coal dust, asbestos, and/or silica.[111] There are no recent data on the frequency of this syndrome; from a risk factor point of view, exposure to inorganic dusts is declining.[111]

### Clinical Presentation

Risk factors for pulmonary rheumatoid nodules include smoking and positive rheumatoid serology.[112] Disease-modifying antirheumatic drugs (DMARDs) including methotrexate, leflunomide, and anti-TNF agents have been associated with the development of pulmonary rheumatoid nodules in case reports and case series.[113–115] Pulmonary rheumatoid nodules are most commonly subpleural in location, and are usually asymptomatic; however, they may present with complications due to cavitation and rupture including pleural effusion, pulmonary abscess, empyema, pneumothorax, and bronchopleural fistula. Pneumothoraces are a rare complication of RA. They are probably the consequence of perforation of cavitating rheumatoid nodules into the pleural space.

### Pathologic Findings

Histology of subcutaneous rheumatoid nodules shows necrotizing granulomas with central fibrinoid necrosis surrounded by palisading macrophages, surrounded by a vascular area containing an inflammatory infiltrate of T lymphocytes and macrophages. Distinct from subcutaneous rheumatoid nodules, pulmonary rheumatoid nodules have also been shown to contain lymphoid aggregates containing B-cells and ectopic lymphoid follicles in the outer rim of the nodule.[116] Histology of nodules in rheumatoid pneumoconiosis is similar except for an additional pigmented dust ring surrounding the lesion.[111]

### Evaluation

An important aspect of evaluating rheumatoid lung nodules is to differentiate them from malignancy and infection. Low uptake on positron emission tomography scanning has been reported with rheumatoid lung nodules, which may help to differentiate them from malignancy. Wherever possible, histology is the most definitive way to differentiate pulmonary rheumatoid nodules from other diagnoses. Incidental lung nodules identified in patients with RA should be worked up in accordance with evidence-based guidelines, such as those from the Fleischner Society.[117]

### Management

Uncomplicated pulmonary rheumatoid nodules do not usually require specific therapy, and they can spontaneously regress. The use of rituximab has been reported to cause a significant reduction in size of pulmonary rheumatoid nodules in case reports and case series.[118,119] Improvement with tocilizumab has also been reported, as well as anti-TNF therapy.[120,121]

For complicated pulmonary rheumatoid nodules, thoracostomy tube insertion is often required for drainage of pneumothoraces and pleural effusions. There is a lack of evidence regarding the management of complicated rheumatoid pleural disease including recurrent pneumothoraces and bronchopleural fistulae, and outcomes following pleurodesis and surgical management may be poor. Evidence-based guidelines for these scenarios are lacking, and treatment decisions are based upon the experience of the clinicians involved.

## Airways Disease in Rheumatoid Arthritis

### Laryngeal Involvement—Cricoarytenoid Arthropathy

Symptoms including dysphonia, foreign body sensation, odynophagia, dysphagia, cough, and dyspnea have been reported in up to two-thirds of patients with RA.[122] The major cause of these problems is cricoarytenoid arthropathy. In mild cases, vocal cord mobility may not be affected and the patient is often asymptomatic; however, in severe cases acute inflammation, or chronic inflammation leading to erosion, subluxation, and ankylosis can occur resulting in impaired mobility of the vocal cords. Severe cricoarytenoid involvement leading to stridor and upper airway obstruction is rare. Other laryngeal structures that can be involved include the cricothyroid joint, vocal folds, recurrent laryngeal nerve, and intrinsic laryngeal muscles.

Pulmonary function testing may show evidence of extrathoracic obstruction. HRCT may reveal evidence of joint involvement including increased joint space due to synovial inflammation, reduced joint space due to degenerative change, increased joint density, ankylosis, erosion, subluxation, and soft tissue swelling. Laryngoscopic findings include edema of the arytenoids and interarytenoid mucosa.[123] Another finding which may be seen is rheumatoid nodules of the vocal folds. Vocal fold nodules in this context are also sometimes referred to as bamboo nodes.

In acute or impending airway obstruction, securement of the airway by tracheostomy is indicated. Cricoarytenoid arthropathy may respond to systemic immunosuppression.[122] Glucocorticoids can also be given locally into the cricoarytenoid joint. Surgical management of airway obstruction by mobilization of the arytenoid cartilages and laterofixation of one of the vocal cords has been reported, and impaired adduction causing aphonia has been successfully managed with adduction surgery.

## Lower Airways Obstructive Disease (Reactive Airways, Obliterative Bronchiolitis, Follicular Bronchiolitis, Bronchiectasis)

### Frequency

Obstructive airways disease is common in RA. Studies of nonsmoking patients with RA have shown an obstructive spirometry pattern, with FEV1/FVC $< 0.7$ in 17.1 and 18% of patients.[124] The lifetime prevalence of developing clinically significant obstructive lung disease as diagnosed by a physician has been reported as 9.6% in patients with RA.[125] A reduction in mean FEV1/FVC and $FEF_{25-75}$ has been reported in patients with RA compared with control subjects.[126] The proportion of patients with bronchial reactivity to methacholine has been reported as 55% in patients with RA, versus 16% in comparator subjects.[126]

### Bronchiectasis

The prevalence of symptomatic bronchiectasis in patients with RA is approximately 3%, which is higher than in the general population which has a prevalence of approximately 0.05%.[127] HRCT studies reveal a prevalence of radiologic evidence of bronchiectasis of up to 35% in patients with RA.[128] Risk factors for the development of bronchiectasis among patients with RA include age, disease duration, and male sex. A multicenter cohort study from Europe found a higher mortality rate in patients with RA and bronchiectasis compared with patients with idiopathic bronchiectasis (OR: 2.03; 95% CI: 1.19–3.44).[129]

There are no specific guidelines for the management of coexisting bronchiectasis and RA. Treatment decisions should be based upon existing guidance for each of these diseases. For patients with severe bronchiectasis, caution should be exercised with more potent immunosuppressive therapies.

### Small Airways Disease (Bronchiolitis)

The small airways of the lung comprise bronchioles without any cartilage with an average internal diameter of 1 mm. In patients with RA, the prevalence of follicular bronchiolitis (FB) ranges from above 5% to less than 65% depending on disease definition, whereas constrictive bronchiolitis (CB, synonymous with obliterative bronchiolitis) is reportedly rare.[130,131] In FB the bronchiole is narrowed due to hyperplasia of bronchial-associated lymphoid tissue, whereas in CB there is concentric bronchiolar fibrosis and no lymphoid hyperplasia. In FB the pulmonary physiology can be restrictive, normal, or obstructive, while in CB the physiology is almost always obstructive.[132] The radiology in FB demonstrates bronchiolar nodularity and bronchial wall thickening, whereas in CB there is mosaic attenuation and gas trapping along with bronchial wall thickening.[133]

It is often difficult to assign causality to underlying RA as patients often have preexisting diagnoses of airways disease related to cigarette smoking, asthma, occupational or drug exposures. As a result the natural history of bronchiolar disease in RA is incompletely characterized and varies from case reports of rapidly progressive CB resulting in respiratory failure and death to a recent case series reporting relative stability of the majority of their patients with OB.[130,131]

The treatment of bronchiolar disease includes inhaled glucocorticosteroids and bronchodilators, macrolides, oral prednisone, and other immunomodulatory treatments targeting underlying inflammation.

### Apical Fibrobullous Disease

Apical fibrobullous disease, usually found in association with ankylosing spondylitis, has also been associated with RA.[134]

### Thoracic Cage Immobility

Altered thoracic cage biomechanics have been demonstrated in patients with RA, resulting in reduced chest expansion, which could contribute to symptoms of dyspnea.[135]

### Venous Thromboembolic Disease

A systematic review and meta-analysis of 10 studies containing 5,273,942 patients with RA found an OR of deep vein thrombosis and/or pulmonary embolus of 2.23 (95% CI: 2.02–2.47), compared with matched controls.[136] This likely reflects hypercoagulability secondary to systemic inflammation.

### Pulmonary Hypertension

The potential causes of pulmonary hypertension in RA include ILD, pulmonary vasculopathy, chronic thromboembolic disease, and left heart disease. Whether pulmonary arterial hypertension is caused by RA remains to be proven. A retrospective study of the French Pulmonary Hypertension Registry found the prevalence of RA to be 0.35% in the cohort overall, and 0.58% in the group classified as idiopathic pulmonary hypertension.[137] This prevalence is similar to the prevalence of RA in the general population, which does not support a specific association between the two conditions.[137] The REVEAL registry, involving 54 centers in the United States, found an overall prevalence of RA of 3.5% among 2,438 consecutive patients identified as having group 1 pulmonary arterial hypertension.[138] A study of 321 Korean patients with connective tissue disease meeting a modified definition of WHO group I pulmonary arterial hypertension reported that 7.8% of patients had RA.[139]

Mild, often subclinical, evidence of elevated pulmonary pressures is commonly found on echocardiography. Echocardiographic studies of patients with RA have found elevated pulmonary artery systolic pressures in 20 to 30% of patients.[140,141] One group of authors determined that this was secondary to lung disease in 6%, cardiac disease in 4%, and 21% had elevated pulmonary artery systolic pressure of 30 mm Hg or more without significant cardiac disease or lung disease detected on lung function tests.[140] Echocardiographic evidence of right ventricular diastolic dysfunction is common in RA, which progresses faster than in the general population, and may reflect myocardial as well as pulmonary disease.[142]

### Vasculitis

Rheumatoid vasculitis is now rare, and most commonly manifests with cutaneous vasculitis and vasculitic neuropathy, although pulmonary angiitis can occur in approximately 1% of cases.[143] The median duration of RA when vasculitis is diagnosed is approximately 10 years; however, pulmonary angiitis as the presenting manifestation of RA has been reported.

### Pulmonary Toxicity of Drugs used to Treat Rheumatoid Arthritis

Methotrexate is recommended by major guidelines as first-line therapy for RA. A meta-analysis of randomized controlled trials found that methotrexate was associated with an increased risk of all adverse respiratory events (relative risk [RR]: 1.10; 95% CI: 1.02–1.19) and respiratory infection (RR: 1.11; 95% CI: 1.02–1.21).[144] A subgroup analysis of studies describing pneumonitis revealed an increased risk associated with methotrexate (RR: 7.81; 95% CI: 1.76–34.72).[144] Prevalence rates of interstitial pneumonitis between 0.3 and 11.6% have been reported.[145] Pulmonary fibrosis and nodulosis have also been observed in methotrexate-treated patients. As nodulosis and fibrosis can be manifestations of RA, it is difficult to ascribe causation to the methotrexate.[145]

To determine if methotrexate is associated with chronic ILD, 55 patients with RA on methotrexate (mean dose: 10.7 mg/week; mean duration: 30 months) were followed for 2 years and compared with 73 control patients with RA not on methotrexate.[146] In total, 20% in the methotrexate group and 23% in the control group had pulmonary fibrosis evident on HRCT at baseline. Serial pulmonary function tests were not different between groups. The authors concluded that there was no evidence that low-dose methotrexate is associated with chronic ILD.[146]

A systematic review of studies reporting pulmonary toxicity of leflunomide found that the rate of noninfectious pulmonary complications varied between 0.02 to 1.2%.[147] Bilateral ground glass opacities and DAD were the most common radiologic and histopathologic findings.[147] An earlier review of 32 reported cases of leflunomide-induced pneumonitis found that cases usually occurred within 20 weeks of initiation of therapy.[148] Two cases had had previous methotrexate-induced pneumonitis, both of whom died. There was a high mortality in patients with DAD on histological examination, preexisting ILD, and ground glass shadowing on HRCT.[148]

Sulfasalazine is a rare cause of specific interstitial pulmonary toxicity. A review of 50 cases found that the most common pathology was eosinophilic pneumonia with peripheral eosinophilia and interstitial inflammation with or without fibrosis.[149]

Anti-TNF therapy has been associated with new onset or exacerbation of ILD in several case reports, as has bronchiolitis obliterans organizing pneumonia.[150] A review of cases of new or worsening ILD after administration of biologic therapies found rituximab has also been associated in a small number of cases.[150] Overall mortality was 29%, and mortality was increased in those receiving immunosuppression, older age, and preexisting ILD.[150] The exact frequency of ILD-related complications of biologic therapies is unknown.

### Lung Cancer

A cohort study of biologic naïve RA subjects in the United Kingdom found that the overall incidence of cancer was increased compared with the general population, and lung cancer had standardized incidence ratio of 2.39 (95% CI: 1.75–3.19).[151] Cancer risk was more than twofold higher in current or ex-smokers than in nonsmokers. A case–control analysis from the U.S. Veteran Affairs database also found that patients with RA were more likely to develop lung cancer after adjusting for age, sex, race, and tobacco and asbestos exposure (OR: 1.43; 95% CI: 1.23–1.65).[152]

### Lung Infections

Results across studies are variable; however, patients with RA are at an overall increased risk of infection due to immune system dysfunction related to the disease itself, comorbidities, and immunosuppressive treatments. Glucocorticoid treatment has been shown to be a particularly important risk factor, increasing the risk for serious infections in a dose-dependent manner approximately two to fourfold, and anti-TNF agents appear to increase the risk just less than twofold compared with conventional DMARD therapy.[153] The risk of infection with anti-TNF agents is highest in the first few months of treatment.

A prospective study of 16,788 patients with RA followed for 3.5 years found increased risk of hospitalization for pneumonia in patients taking prednisone (HR: 1.7; 95% CI: 1.5–2.0) and leflunomide (HR: 1.2; 95% CI: 1.0–1.5), but not sulfasalazine, methotrexate, etanercept, infliximab, or adalimumab.[154] Data from a population-based study of patients with RA reported that higher infection rates were observed among patients with RA-ILD during the first year after ILD diagnosis (14.1 per 100 person years, py) than subsequently (5.7 per 100 py; $p = 0.001$).[155] Pneumonia was the most common (3.9 per 100 py of follow-up). Overall infection risk was higher in OP (27.1 per 100 py) than UIP (7.7 per 100 py) or NSIP (5.5 per 100 py; $p < 0.001$). The highest infection rate observed was with a daily prednisone use >10 mg per day (15.4 per 100 py).[155]

It is recommended that patients with RA receive screening for latent or active tuberculosis prior to commencing biologic therapy or Janus kinase inhibitors, and all patients on DMARD therapy receive vaccination against pneumococcal disease and influenza.[156] Prophylaxis against *Pneumocystis jiroveci* may be indicated in certain situations. An observational study of 1,092 patients with a range of rheumatological conditions who received 1,522 "treatment episodes," defined as more than 4 weeks of ≥ 30 mg of prednisone per day, for more than 4 weeks showed a reduced 1-year incidence of pneumocystis pneumonia in patients receiving prophylactic trimethoprim/sulfamethoxazole (HR: 0.07; 95% CI: 0.01–0.53).[157] In total, 68 of the 1,522 treatment episodes were in patients with RA. The risk of pneumocystis pneumonia in rheumatoid patients was lower than in other conditions such as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.[157]

## Summary

Lung disease occurring in patients with RA is due to the systemic inflammatory nature of the disease. Respiratory manifestations are manifold, and especially parenchymal disease may be associated with increased premature mortality. Management is generally directed toward reduction of systemic inflammation, with specific treatment for complications such as cricoarytenoid involvement and plural disease. Management of interstitial disease remains challenging; better understanding of the disease pathobiology may provide insights for both the causes and treatment of RA and its associated lung disease.

Conflict of Interest
None.

## References

1 Myasoedova E, Crowson CS, Turesson C, Gabriel SE, Matteson EL. Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995-2007 versus 1985-1994: a population-based study. J Rheumatol 2011;38(06):983–989
2 Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010;62(06):1583–1591
3 Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med 2011;183(03):372–378
4 Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. Thorax 2001;56(08):622–627
5 Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997;156 (2, Pt 1):528–535
6 Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med 2008;168(02):159–166
7 Saag KG, Kolluri S, Koehnke RK, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. Arthritis Rheum 1996;39(10):1711–1719
8 Giles JT, Danoff SK, Sokolove J, et al. Association of fine specificity and repertoire expansion of anticitrullinated peptide antibodies with rheumatoid arthritis associated interstitial lung disease. Ann Rheum Dis 2014;73(08):1487–1494
9 Gilligan DM, O'Connor CM, Ward K, Moloney D, Bresnihan B, FitzGerald MX. Bronchoalveolar lavage in patients with mild and severe rheumatoid lung disease. Thorax 1990;45(08):591–596
10 Yin Y, Liang D, Zhao L, et al. Anti-cyclic citrullinated peptide antibody is associated with interstitial lung disease in patients with rheumatoid arthritis. PLoS One 2014;9(04):e92449
11 Mori S, Koga Y, Sugimoto M. Different risk factors between interstitial lung disease and airway disease in rheumatoid arthritis. Respir Med 2012;106(11):1591–1599
12 Bartels CM, Bell CL, Shinki K, Rosenthal A, Bridges AJ. Changing trends in serious extra-articular manifestations of rheumatoid arthritis among United State veterans over 20 years. Rheumatology (Oxford) 2010;49(09):1670–1675
13 Cavagna L, Monti S, Grosso V, et al. The multifaceted aspects of interstitial lung disease in rheumatoid arthritis. BioMed Res Int 2013;2013:759760
14 Lee HK, Kim DS, Yoo B, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest 2005;127(06):2019–2027
15 Zrour SH, Touzi M, Bejia I, et al. Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis. Prospective study in 75 patients. Joint Bone Spine 2005;72(01):41–47
16 Brown KK. Rheumatoid lung disease. Proc Am Thorac Soc 2007;4 (05):443–448
17 Jacob J, Hirani N, van Moorsel CHM, et al. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. Eur Respir J 2019;53(01):1800869
18 Zhang Y, Li H, Wu N, Dong X, Zheng Y. Retrospective study of the clinical characteristics and risk factors of rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol 2017;36(04): 817–823
19 Krause ML, Zamora AC, Vassallo R, Ryu JH, Matteson EL. The lung disease of rheumatoid arthritis. Curr Respir Med Rev 2015;11 (02):119–129

20 Shidara K, Hoshi D, Inoue E, et al. Incidence of and risk factors for interstitial pneumonia in patients with rheumatoid arthritis in a large Japanese observational cohort, IORRA. Mod Rheumatol 2010;20(03):280–286

21 Koduri G, Norton S, Young A, et al; ERAS (Early Rheumatoid Arthritis Study). Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford) 2010;49(08):1483–1489

22 Kelly CA, Saravanan V, Nisar M, et al; British Rheumatoid Interstitial Lung (BRILL) Network. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics–a large multicentre UK study. Rheumatology (Oxford) 2014;53(09):1676–1682

23 Bernstein EJ, Barr RG, Austin JHM, et al. Rheumatoid arthritis-associated autoantibodies and subclinical interstitial lung disease: the Multi-Ethnic Study of Atherosclerosis. Thorax 2016;71 (12):1082–1090

24 Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis 1997;56(08):463–469

25 Richman NC, Yazdany J, Graf J, Chernitskiy V, Imboden JB. Extraarticular manifestations of rheumatoid arthritis in a multiethnic cohort of predominantly Hispanic and Asian patients. Medicine (Baltimore) 2013;92(02):92–97

26 Murphy D, Hutchinson D. Is male rheumatoid arthritis an occupational disease? A review. Open Rheumatol J 2017;11:88–105

27 Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. Lancet 2009;373(9664):659–672

28 Solomon JJ, Chung JH, Cosgrove GP, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016;47(02):588–596

29 Mikuls TR, Payne JB, Deane KD, Thiele GM. Autoimmunity of the lung and oral mucosa in a multisystem inflammatory disease: the spark that lights the fire in rheumatoid arthritis? J Allergy Clin Immunol 2016;137(01):28–34

30 Bongartz T, Cantaert T, Atkins SR, et al. Citrullination in extra-articular manifestations of rheumatoid arthritis. Rheumatology (Oxford) 2007;46(01):70–75

31 Willis VC, Demoruelle MK, Derber LA, et al. Sputum autoantibodies in patients with established rheumatoid arthritis and subjects at risk of future clinically apparent disease. Arthritis Rheum 2013;65(10):2545–2554

32 Quirke AM, Perry E, Cartwright A, et al. Bronchiectasis is a model for chronic bacterial infection inducing autoimmunity in rheumatoid arthritis. Arthritis Rheumatol 2015;67(09):2335–2342

33 Padyukov L, Silva C, Stolt P, Alfredsson L, Klareskog L. A gene-environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. Arthritis Rheum 2004;50(10):3085–3092

34 Van Hove CL, Moerloose K, Maes T, Joos GF, Tournoy KG. Cigarette smoke enhances Th-2 driven airway inflammation and delays inhalational tolerance. Respir Res 2008;9:42

35 Vassallo R, Walters PR, Lamont J, Kottom TJ, Yi ES, Limper AH. Cigarette smoke promotes dendritic cell accumulation in COPD; a Lung Tissue Research Consortium study. Respir Res 2010;11:45

36 Checa M, Hagood JS, Velazquez-Cruz R, et al. Cigarette smoke enhances the expression of profibrotic molecules in alveolar epithelial cells. PLoS One 2016;11(03):e0150383

37 Sendo S, Saegusa J, Okano T, Takahashi S, Akashi K, Morinobu A. CD11b+Gr-1(dim) tolerogenic dendritic cell-like cells are expanded in interstitial lung disease in SKG mice. Arthritis Rheumatol 2017;69(12):2314–2327

38 Nguyen NT, Hanieh H, Nakahama T, Kishimoto T. The roles of aryl hydrocarbon receptor in immune responses. Int Immunol 2013; 25(06):335–343

39 Makrygiannakis D, Hermansson M, Ulfgren AK, et al. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann Rheum Dis 2008;67(10):1488–1492

40 Lee J, Luria A, Rhodes C, et al. Nicotine drives neutrophil extracellular traps formation and accelerates collagen-induced arthritis. Rheumatology (Oxford) 2017;56(04):644–653

41 Vassallo R, Luckey D, Behrens M, et al. Cellular and humoral immunity in arthritis are profoundly influenced by the interaction between cigarette smoke effects and host HLA-DR and DQ genes. Clin Immunol 2014;152(1–2):25–35

42 Scher JU, Joshua V, Artacho A, et al. The lung microbiota in early rheumatoid arthritis and autoimmunity. Microbiome 2016;4 (01):60

43 Mikuls TR, Payne JB, Yu F, et al. Periodontitis and Porphyromonas gingivalis in patients with rheumatoid arthritis. Arthritis Rheumatol 2014;66(05):1090–1100

44 Bidkar M, Vassallo R, Luckey D, Smart M, Mouapi K, Taneja V. Cigarette smoke induces immune responses to vimentin in both arthritis-susceptible and -resistant humanized mice. PLoS One 2016;11(09):e0162341

45 Snir O, Rieck M, Gebe JA, et al. Identification and functional characterization of T cells reactive to citrullinated vimentin in HLA-DRB1*0401-positive humanized mice and rheumatoid arthritis patients. Arthritis Rheum 2011;63(10):2873–2883

46 Reynisdottir G, Karimi R, Joshua V, et al. Structural changes and antibody enrichment in the lungs are early features of anti-citrullinated protein antibody-positive rheumatoid arthritis. Arthritis Rheumatol 2014;66(01):31–39

47 Clavel C, Nogueira L, Laurent L, et al. Induction of macrophage secretion of tumor necrosis factor α through Fcgamma receptor IIa engagement by rheumatoid arthritis-specific autoantibodies to citrullinated proteins complexed with fibrinogen. Arthritis Rheum 2008;58(03):678–688

48 Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A, et al. NETs are a source of citrullinated autoantigens and stimulate inflammatory responses in rheumatoid arthritis. Sci Transl Med 2013;5 (178):178ra40

49 Schafer MJ, White TA, Iijima K, et al. Cellular senescence mediates fibrotic pulmonary disease. Nat Commun 2017;8:14532

50 Fujii H, Shao L, Colmegna I, Goronzy JJ, Weyand CM. Telomerase insufficiency in rheumatoid arthritis. Proc Natl Acad Sci U S A 2009;106(11):4360–4365

51 Juge PA, Borie R, Kannengiesser C, et al; FREX consortium. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. Eur Respir J 2017;49 (05):1602314

52 Seibold MA, Wise AL, Speer MC, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med 2011;364(16):1503–1512

53 Borie R, Crestani B, Dieude P, et al. The MUC5B variant is associated with idiopathic pulmonary fibrosis but not with systemic sclerosis interstitial lung disease in the European Caucasian population. PLoS One 2013;8(08):e70621

54 Johnson C, Rosen P, Lloyd T, et al. Exploration of the MUC5B promoter variant and ILD risk in patients with autoimmune myositis. Respir Med 2017;130:52–54

55 Juge PA, Lee JS, Ebstein E, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. N Engl J Med 2018;379(23):2209–2219

56 Mangan PR, Harrington LE, O'Quinn DB, et al. Transforming growth factor-beta induces development of the T(H)17 lineage. Nature 2006;441(7090):231–234

57 Hara M, Kono H, Furuya S, Hirayama K, Tsuchiya M, Fujii H. Interleukin-17A plays a pivotal role in cholestatic liver fibrosis in mice. J Surg Res 2013;183(02):574–582

58 Doyle TJ, Patel AS, Hatabu H, et al. Detection of rheumatoid arthritis-interstitial lung disease is enhanced by serum biomarkers. Am J Respir Crit Care Med 2015;191(12):1403–1412

59 Putman RK, Hatabu H, Araki T, et al; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators; COPDGene Investigators. Association between interstitial lung abnormalities and all-cause mortality. JAMA 2016;315(07):672–681

60 Travis WD, Costabel U, Hansell DM, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. 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 (06):733–748

61 Doyle TJ, Dellaripa PF. Lung manifestations in the rheumatic diseases. Chest 2017;152(06):1283–1295

62 Hyldgaard C, Hilberg O, Pedersen AB, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis 2017;76 (10):1700–1706

63 Sgalla G, Larici AR, Sverzellati N, et al. Quantitative analysis of lung sounds for monitoring idiopathic pulmonary fibrosis: a prospective pilot study. Eur Respir J 2018. doi: 10.1183/ 13993003.02093-2018

64 Spagnolo P, Lee JS, Sverzellati N, Rossi G, Cottin V. The lung in rheumatoid arthritis - focus on interstitial lung disease. Arthritis Rheumatol 2018;70(10):1544–1554

65 Saketkoo LA, Matteson EL, Brown KK, Seibold JR, Strand V; Connective Tissue Disease-related Interstitial Lung Disease Special Interest Group. Developing disease activity and response criteria in connective tissue disease-related interstitial lung disease. J Rheumatol 2011;38(07):1514–1518

66 Khanna D, Mittoo S, Aggarwal R, et al. Connective tissue disease-associated interstitial lung diseases: report from OMERACT CTD-ILD Working Group. J Rheumatol 2015;42(11):2168–2171

67 Rajasekaran BA, Shovlin D, Lord P, Kelly CA. Interstitial lung disease in patients with rheumatoid arthritis: a comparison with cryptogenic fibrosing alveolitis. Rheumatology (Oxford) 2001;40 (09):1022–1025

68 Ito Y, Arita M, Kumagai S, et al. Radiological fibrosis score is strongly associated with worse survival in rheumatoid arthritis-related interstitial lung disease. Mod Rheumatol 2019;29(01): 98–104

69 Assayag D, Lubin M, Lee JS, King TE, Collard HR, Ryerson CJ. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. Respirology 2014;19(04):493–500

70 Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology (Oxford) 2017;56(03):344–350

71 Bradley B, Branley HM, Egan JJ, et al; British Thoracic Society Interstitial Lung Disease Guideline Group, British Thoracic Society Standards of Care Committee; Thoracic Society of Australia; New Zealand Thoracic Society; Irish Thoracic Society. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008;63(Suppl 5): v1–v58

72 Jani M, Dixon W, Matteson EL. Management of the patient with rheumatoid arthritis and interstitial lung disease. In: Fischer A, Lee J, eds. Lung Disease in Rheumatoid Arthritis. New York, NY: Humana Press (Springer); 2018:121–161

73 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(03): 236–245

74 Wells AU, Denton CP. Interstitial lung disease in connective tissue disease–mechanisms and management. Nat Rev Rheumatol 2014;10(12):728–739

75 Kouranos V, Miranda G, Corte TJ, Renzoni EA. New treatment paradigms for connective tissue disease-associated interstitial lung disease. Curr Opin Pulm Med 2018;24(05):453–460

76 Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ; Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366(21):1968–1977

77 Song JW, Lee HK, Lee CK, et al. Clinical course and outcome of rheumatoid arthritis-related usual interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis 2013;30(02):103–112

78 Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis associated interstitial lung disease. Arthritis Rheumatol 2017; 69(03):542–549

79 Jani M, Hirani N, Matteson EL, Dixon WG. The safety of biologic therapies in RA-associated interstitial lung disease. Nat Rev Rheumatol 2014;10(05):284–294

80 Richeldi L, du Bois RM, Raghu G, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370(22):2071–2082

81 King TE Jr, Bradford WZ, Castro-Bernardini S, et al; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370(22): 2083–2092

82 Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ; IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. Eur Respir J 2018; 51(05):1800692

83 ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/ show/NCT02808871. Accessed March 4, 2019

84 Cho J, Zhou J, Lo D, Mak A, Tay SH. Palliative and end-of-life care in rheumatology: high symptom prevalence and unmet needs. Semin Arthritis Rheum 2018 (e-pub ahead of print). Doi: 10.1016/j.semarthrit.2018.10.020

85 Luckett T, Phillips J, Johnson MJ, et al. Contributions of a hand-held fan to self-management of chronic breathlessness. Eur Respir J 2017;50(02):1700262

86 Smallwood N, Thompson M, Warrender-Sparkes M, et al. Integrated respiratory and palliative care may improve outcomes in advanced lung disease. ERJ Open Res 2018;4(01):00102–02017

87 Kreuter M, Bendstrup E, Russell AM, et al. Palliative care in interstitial lung disease: living well. Lancet Respir Med 2017;5 (12):968–980

88 Courtwright AM, El-Chemaly S, Dellaripa PF, Goldberg HJ. Survival and outcomes after lung transplantation for non-scleroderma connective tissue-related interstitial lung disease. J Heart Lung Transplant 2017;36(07):763–769

89 Yazdani A, Singer LG, Strand V, Gelber AC, Williams L, Mittoo S. Survival and quality of life in rheumatoid arthritis-associated interstitial lung disease after lung transplantation. J Heart Lung Transplant 2014;33(05):514–520

90 Jurik AG, Davidsen D, Graudal H. Prevalence of pulmonary involvement in rheumatoid arthritis and its relationship to some characteristics of the patients. A radiological and clinical study. Scand J Rheumatol 1982;11(04):217–224

91 Talbott JA, Calkins E. Pulmonary involvement in rheumatoid Arthritis. JAMA 1964;189(12):911–913

92 Horler AR, Thompson M. The pleural and pulmonary complications of rheumatoid arthritis. Ann Intern Med 1959;51(06): 1179–1203

93 Walker WC, Wright V. Rheumatoid pleuritis. Ann Rheum Dis 1967;26(06):467–474

94 Jurik AG, Graudal H. Pleurisy in rheumatoid arthritis. Scand J Rheumatol 1983;12(02):75–80

95 Balbir-Gurman A, Yigla M, Nahir AM, Braun-Moscovici Y. Rheumatoid pleural effusion. Semin Arthritis Rheum 2006;35(06): 368–378

96 Hakala M, Tiilikainen A, Hämeenkorpi R, et al. Rheumatoid arthritis with pleural effusion includes a subgroup with autoimmune features and HLA-B8, Dw3 association. Scand J Rheumatol 1986;15(03):290–296

97 Allan JS, Donahue DM, Garrity JM. Rheumatoid pleural effusion in the absence of arthritic disease. Ann Thorac Surg 2005;80(04): 1519–1521

98 Russell ML, Gladman DD, Mintz S. Rheumatoid pleural effusion: lack of response to intrapleural corticosteroid. J Rheumatol 1986;13(02):412–415

99 Faurschou P, Francis D, Faarup P. Thoracoscopic, histological, and clinical findings in nine case of rheumatoid pleural effusion. Thorax 1985;40(05):371–375

100 Shinto R, Prete P. Characteristic cytology in rheumatoid pleural effusion. Am J Med 1988;85(04):587–589

101 Pettersson T, Klockars M, Hellström PE. Chemical and immunological features of pleural effusions: comparison between rheumatoid arthritis and other diseases. Thorax 1982;37(05): 354–361

102 Pereyra MF, Ferreiro L, Valdés L. Unexpandable lung. Arch Bronconeumol 2013;49(02):63–69

103 Jones FL Jr, Blodgett RC Jr. Empyema in rheumatoid pleuropulmonary disease. Ann Intern Med 1971;74(05):665–671

104 Sahn SA, Kaplan RL, Maulitz RM, Good JT Jr. Rheumatoid pleurisy. observations on the development of low pleural fluid pH and glucose level. Arch Intern Med 1980;140(09):1237–1238

105 Wrightson JM, Stanton AE, Maskell NA, Davies RJO, Lee YCG. Pseudochylothorax without pleural thickening: time to reconsider pathogenesis? Chest 2009;136(04):1144–1147

106 Chapman PT, O'Donnell JL, Moller PW. Rheumatoid pleural effusion: response to intrapleural corticosteroid. J Rheumatol 1992;19(03):478–480

107 Fujita S, Mukai T, Akagi T, Morita Y. Treatment of refractory rheumatoid pleural effusion with abatacept. BMJ Case Rep 2018. Doi: 10.1136/bcr-2017-224034

108 Ohtsuka K, Takeuchi K, Matsushita M, Aramaki T. A case of bilateral rheumatoid pleuritis successfully treated with tocilizumab. Mod Rheumatol 2014;24(06):1001–1004

109 Patil M, Dhillon SS, Attwood K, Saoud M, Alraiyes AH, Harris K. Management of benign pleural effusions using indwelling pleural catheters. Chest 2017;151(03):626–635

110 Cortet B, Perez T, Roux N, et al. Pulmonary function tests and high resolution computed tomography of the lungs in patients with rheumatoid arthritis. Ann Rheum Dis 1997;56(10):596–600

111 Schreiber J, Koschel D, Kekow J, Waldburg N, Goette A, Merget R. Rheumatoid pneumoconiosis (Caplan's syndrome). Eur J Intern Med 2010;21(03):168–172

112 Koslow M, Young JR, Yi ES, et al. Rheumatoid pulmonary nodules: clinical and imaging features compared with malignancy. Eur Radiol 2019;29:1684–1692

113 Balkarli A, Cobankara V. Pulmonary nodulosis associated with leflunomide therapy in rheumatoid arthritis: report of four cases and review of the literature. J Clin Exp Invest 2016;7(01):98–102

114 Steeghs N, Huizinga TW, Dik H. Bilateral hydropneumothoraces in a patient with pulmonary rheumatoid nodules during treatment with methotrexate. Ann Rheum Dis 2005;64(11):1661–1662

115 Toussirot E, Berthelot JM, Pertuiset E, et al. Pulmonary nodulosis and aseptic granulomatous lung disease occurring in patients with rheumatoid arthritis receiving tumor necrosis factor-alpha-blocking agent: a case series. J Rheumatol 2009;36(11): 2421–2427

116 Highton J, Hung N, Hessian P, Wilsher M. Pulmonary rheumatoid nodules demonstrating features usually associated with rheumatoid synovial membrane. Rheumatology (Oxford) 2007;46 (05):811–814

117 MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology 2017;284(01): 228–243

118 Glace B, Gottenberg JE, Mariette X, et al. Efficacy of rituximab in the treatment of pulmonary rheumatoid nodules: findings in 10 patients from the French AutoImmunity and Rituximab/Rheumatoid Arthritis registry (AIR/PR registry). Ann Rheum Dis 2012; 71(08):1429–1431

119 Sargin G, Senturk T. Multiple pulmonary rheumatoid nodules. Reumatologia 2015;53(05):276–278

120 Andres M, Vela P, Romera C. Marked improvement of lung rheumatoid nodules after treatment with tocilizumab. Rheumatology (Oxford) 2012;51(06):1134–1136

121 Derot G, Marini-Portugal A, Maitre B, Claudepierre P. Marked regression of pulmonary rheumatoid nodules under etanercept therapy. J Rheumatol 2009;36(02):437–439

122 Bozbas G, Gunel C, Gurer G, Karatas R, Ermisler B. An often overlooked joint in rheumatoid arthritis: cricoarytenoid joint. Biomed Res 2017;28(04):1733–1737

123 Huang K, Kur J. Laryngeal stridor in rheumatoid arthritis. CMAJ 2017;189(38):E1213

124 Fuld JP, Johnson MK, Cotton MM, et al. A longitudinal study of lung function in nonsmoking patients with rheumatoid arthritis. Chest 2003;124(04):1224–1231

125 Nannini C, Medina-Velasquez YF, Achenbach SJ, et al. Incidence and mortality of obstructive lung disease in rheumatoid arthritis: a population-based study. Arthritis Care Res (Hoboken) 2013;65(08):1243–1250

126 Hassan WU, Keaney NP, Holland CD, Kelly CA. Bronchial reactivity and airflow obstruction in rheumatoid arthritis. Ann Rheum Dis 1994;53(08):511–514

127 Wilczynska MM, Condliffe AM, McKeon DJ. Coexistence of bronchiectasis and rheumatoid arthritis: revisited. Respir Care 2013;58(04):694–701

128 Mohd Noor N, Mohd Shahrir MS, Shahid MS, Abdul Manap R, Shahizon Azura AM, Azhar Shah S. Clinical and high resolution computed tomography characteristics of patients with rheumatoid arthritis lung disease. Int J Rheum Dis 2009;12(02):136–144

129 De Soyza A, McDonnell MJ, Goeminne PC, et al. Bronchiectasis rheumatoid overlap syndrome is an independent risk factor for mortality in patients with bronchiectasis: a multicenter cohort study. Chest 2017;151(06):1247–1254

130 Devouassoux G, Cottin V, Lioté H, et al; Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis. Eur Respir J 2009;33(05):1053–1061

131 Lin E, Limper AH, Moua T. Obliterative bronchiolitis associated with rheumatoid arthritis: analysis of a single-center case series. BMC Pulm Med 2018;18(01):105

132 Tashtoush B, Okafor NC, Ramirez JF, Smolley L. Follicular bronchiolitis: a literature review. J Clin Diagn Res 2015;9(09):OE01–OE05

133 Yuksekkaya R, Celikyay F, Yilmaz A, et al. Pulmonary involvement in rheumatoid arthritis: multidetector computed tomography findings. Acta Radiol 2013;54(10):1138–1149

134 Petrie JP, Caughey DE. Bilateral apical fibrobullous disease complicated by bilateral Aspergillus mycetomata in rheumatoid arthritis. N Z Med J 1983;96(723):7–8

135 Bégin R, Radoux V, Cantin A, Ménard HA. Stiffness of the rib cage in a subset of rheumatoid patients. Hai 1988;166(03):141–148

136 Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. Arthritis Res Ther 2014;16(05):435

137 Montani D, Henry J, O'Connell C, et al. Association between rheumatoid arthritis and pulmonary hypertension: data from the French Pulmonary Hypertension Registry. Respiration 2018; 95(04):244–250

138 Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010;137(02):376–387

139 Jeon CH, Chai JY, Seo YI, Jun JB, Koh EM, Lee SK; pulmonary hypertension study group of Korean College of Rheumatology. Pulmonary hypertension associated with rheumatic diseases: baseline characteristics from the Korean registry. Int J Rheum Dis 2012;15(05):e80–e89

140 Dawson JK, Goodson NG, Graham DR, Lynch MP. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. Rheumatology (Oxford) 2000; 39(12):1320–1325
141 Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, et al. Echocardiographic and Doppler findings in long-term treated rheumatoid arthritis patients without clinically evident cardiovascular disease. Semin Arthritis Rheum 2004;33(04):231–238
142 Davis JM III, Lin G, Oh JK, et al. Five-year changes in cardiac structure and function in patients with rheumatoid arthritis compared with the general population. Int J Cardiol 2017; 240:379–385
143 Makol A, Crowson CS, Wetter DA, Sokumbi O, Matteson EL, Warrington KJ. Vasculitis associated with rheumatoid arthritis: a case-control study. Rheumatology (Oxford) 2014;53(05):890–899
144 Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheumatol 2014;66 (04):803–812
145 Barrera P, Laan RF, van Riel PL, Dekhuijzen PN, Boerbooms AMT, van de Putte LB. Methotrexate-related pulmonary complications in rheumatoid arthritis. Ann Rheum Dis 1994;53(07):434–439
146 Dawson JK, Graham DR, Desmond J, Fewins HE, Lynch MP. Investigation of the chronic pulmonary effects of low-dose oral methotrexate in patients with rheumatoid arthritis: a prospective study incorporating HRCT scanning and pulmonary function tests. Rheumatology (Oxford) 2002;41(03):262–267
147 Raj R, Nugent K. Leflunomide-induced interstitial lung disease (a systematic review). Sarcoidosis Vasc Diffuse Lung Dis 2013;30 (03):167–176
148 Chikura B, Lane S, Dawson JK. Clinical expression of leflunomide-induced pneumonitis. Rheumatology (Oxford) 2009;48(09): 1065–1068
149 Parry SD, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. Eur Respir J 2002;19(04):756–764
150 Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum 2011;41(02):256–264
151 Mercer LK, Davies R, Galloway JB, et al; British Society for Rheumatology Biologics Register (BSRBR) Control Centre Consortium. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. Rheumatology (Oxford) 2013;52(01):91–98
152 Khurana R, Wolf R, Berney S, Caldito G, Hayat S, Berney SM. Risk of development of lung cancer is increased in patients with rheumatoid arthritis: a large case control study in US veterans. J Rheumatol 2008;35(09):1704–1708
153 Strangfeld A, Eveslage M, Schneider M, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 2011;70 (11):1914–1920
154 Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum 2006;54(02): 628–634
155 Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol 2016;35(10): 2585–2589
156 Singh JA, Saag KG, Bridges SL Jr, et al; American College of Rheumatology. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68(01):1–25
157 Park JW, Curtis JR, Moon J, Song YW, Kim S, Lee EB. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. Ann Rheum Dis 2018;77 (05):644–649