

Article

# The effects of RA on the lungs

The lungs can be affected in RA through the RA itself, or as an effect from treatment given for RA.

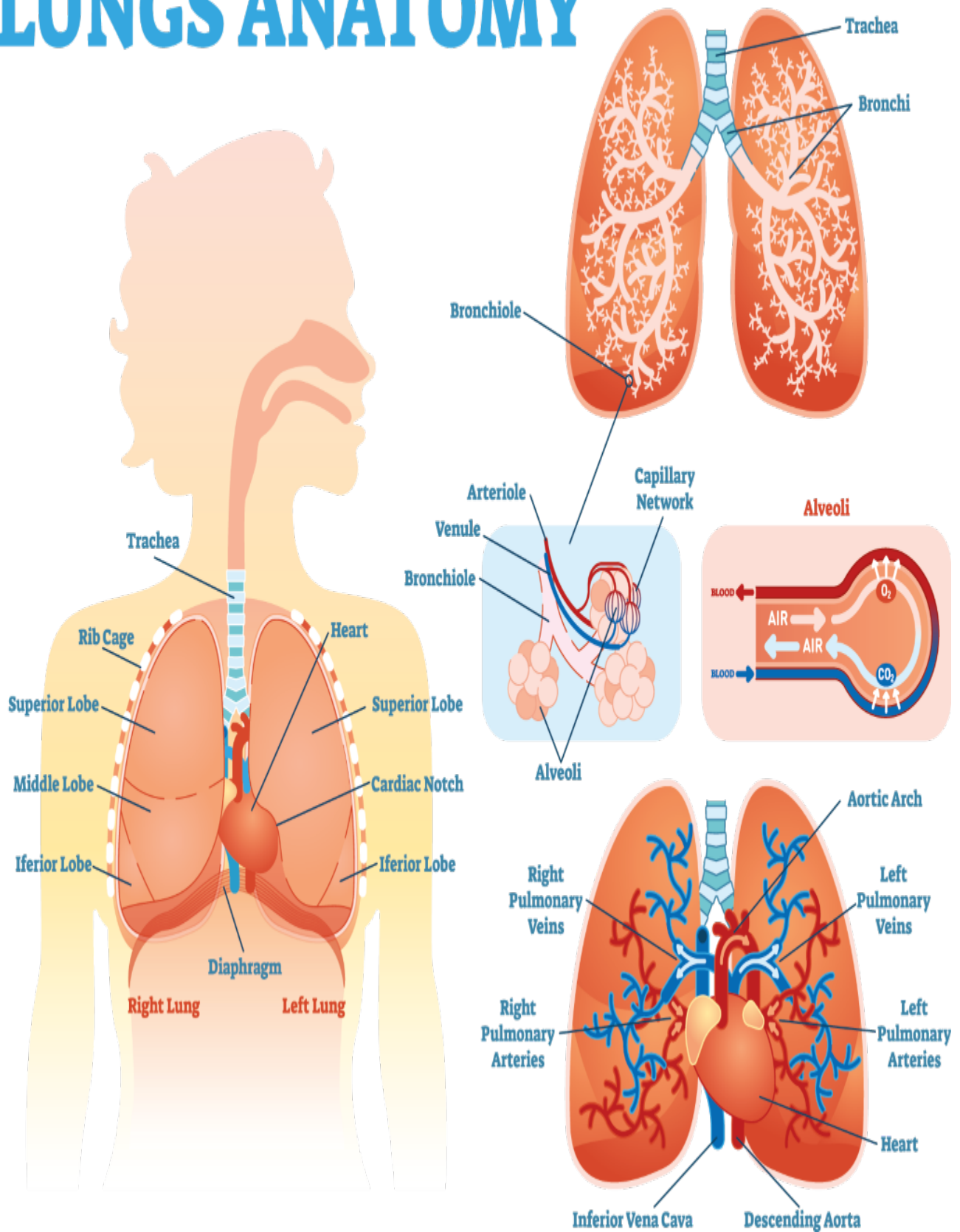
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There are three situations in which the lung can be adversely affected in people with rheumatoid arthritis:

1. A direct effect of rheumatoid disease on the lungs
2. An adverse effect of treatment given for rheumatoid on lung tissue
3. Chest infections, as a consequence of rheumatoid itself or the immune-suppressing therapies given to treat it, causing a further deterioration in lung function

This article aims to give an overview of these three ways in which the lungs can be affected.

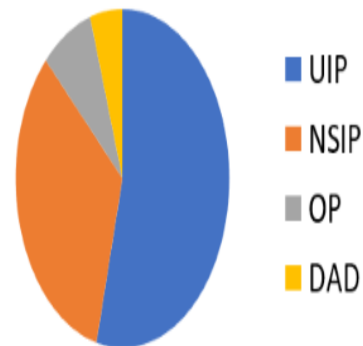
# LUNGS ANATOMY



## 1. The direct effects of rheumatoid disease on lung tissue and pleura

People with RA can develop disease in their lungs, as a consequence of their immune system attacking their joints and other tissues. Different types of lung disease can occur, including interstitial lung disease (ILD), bronchiectasis and bronchiolitis obliterans. In each of these, inflammation and damage can occur to the lung tissue, reducing the ability to absorb oxygen from the air we breathe into the bloodstream and causing breathlessness in affected people. Often this is accompanied by a persistent cough, especially with exertion. Breathing tests (also called lung function or pulmonary function tests) and a CT scan of the lungs are used to confirm the diagnosis, and precise patterns of lung disease are described.

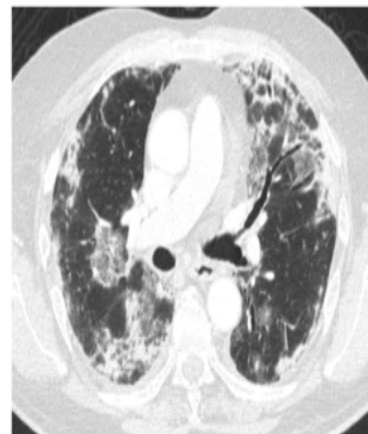
### HR CT types of RA-ILD



**UIP:** 44-66%  
Usual  
interstitial  
pneumonia



**NSIP:** 24-44%  
Non specific  
interstitial  
pneumonia



**OP:** <10%  
Organising  
pneumonia



**DAD:** <5%  
Diffuse  
Alveolar  
Damage

## Interstitial lung disease (ILD)

In interstitial lung disease (ILD) immune cells collect in the lung, accompanied by thickening or fibrosis of the tissues. This means the air sacs (alveoli) are less able to absorb the oxygen we breathe into the bloodstream. Although CT scans show evidence of ILD in a high proportion of RA patients (over half in some studies), this is not sufficiently extensive to cause breathlessness or cough in most, with symptoms estimated to occur in as few as 5% of RA patients. The CT appearances are so characteristic that radiologists are able to describe four patterns of ILD, listed below in order of how common they are:

- interstitial pneumonia (UIP) – the commonest form
- non-specific interstitial pneumonia (NSIP)
- organising pneumonia (OP) and diffuse alveolar damage (DAD) – much less frequent

RA patients who are more likely to develop ILD include:

- those that have smoked
- have rheumatoid nodules
- developed RA at a relatively older age
- have rheumatoid factor and anti-CCP antibodies
- are male

Usually, ILD develops several years after the RA diagnosis, but up to a quarter of RA patients have ILD from when they first develop RA, or even before their joints are affected. Historically there was no treatment for ILD and survival was poor, this being the second commonest cause of premature death (after cardiovascular problems such as heart attacks and strokes) in people with RA. However, more help is available now and there is evidence that some therapies, including mycophenolate mofetil, rituximab and abatacept, slow down or even prevent ILD progression.

## Bronchiectasis

Bronchiectasis is a condition in which the branches of the airways are widened. This can occur as a consequence of recurrent infections or because they are pulled apart from fibrosis, as occurs in ILD. The consequence is that mucus and secretions collect within the airways, rather than being coughed up. Retention of secretions is a problem because this reduces the flow of air and hence oxygen absorption, making the affected person breathless on exertion. Retained secretions also encourage bacteria to grow, making chest infections more likely, and in the most extensive cases, these become a recurring problem. As in ILD, features are more commonly seen on CT than reported by patients, with up to 30% having areas of bronchiectasis but far fewer having symptoms. There are some chicken and egg theories concerning bronchiectasis and RA with thoughts that the bacteria in bronchiectasis are a cause of CCP antibodies which then trigger the onset of RA, and alternatively that the immune suppression used to treat RA leads to recurrent chest infections which ultimately result in bronchiectasis.

## Bronchiolitis obliterans

Bronchiolitis obliterans is another inflammatory condition, in which the smallest airways (bronchioles) become blocked or obstructed. This means there is less airflow to the air sacs and so less absorption of oxygen. The affected person feels breathless and may have a cough and be wheezy. This condition is more commonly seen as a result of inhaling chemicals, such as diacetyl used as a flavouring in microwave popcorn and e-cigarettes, but rarely may also occur in people with RA. In contrast to ILD, symptoms can commence over a short period of time, get worse quickly, and in the absence of reversible treatment, the most severe cases may require lung transplantation.

The pleura is a double-layered envelope surrounding the lungs. In some people with RA, the pleural layers can be affected by inflammation, leading to thickening of the pleural tissue and fluid collecting in the pleural space. This is more likely to occur in men and people with rheumatoid nodules. Pleural thickening and fluid may occur around one or both lungs, and whilst there are signs of this in over half of all RA patients on CT scans, in the majority, the extent is mild and far less than 10% have pain or breathlessness from pleural disease. Often investigations have to be done to confirm the diagnosis, requiring the fluid to be sampled and a pleural biopsy is taken to distinguish rheumatoid pleural fluid from infection (bacteria or tuberculosis) or cancer. Standard treatments for RA are usually effective for pleural disease, and only very rarely is surgery necessary to prevent fluid collecting.

Nodules are a feature of RA and can occur within the lung or on the pleura. They are collections of immune cells, often found at the back of the elbow, and whilst a sign that the immune system is over-active (part of the RA disease process), the nodules themselves rarely cause symptoms and generally do no harm. When present in the lung, they can be solitary or multiple and range in size from a few millimetres to several centimetres when they can be visible on a chest X-ray. Although they have some characteristic features on CT and PET scans, sometimes a biopsy (small tissue sample) has to be taken to confirm the diagnosis, as they can look the same as cancer. Methotrexate treatment can make rheumatoid nodules larger and more numerous, whereas other therapies, including rituximab and JAK inhibitors, are effective in shrinking them.

## 2. The effects of RA treatment on lung tissue or the pleura

In principle, any medication that effectively suppresses the immune driven inflammatory processes that cause RA should also be effective for all manifestations of the disease, in all organs. This is generally true, with many instances in which the early signs of lung or pleural disease on CT scan never progress to the extent that the affected person becomes breathless or develops a cough, because of the effectiveness of the medications they are taking. Nonetheless, when RA lung disease is found to get worse, it can be hard to decide if this is because the existing therapy is not completely effective at suppressing the inflammatory RA process or alternatively because the therapy itself is having a direct toxic effect on the lung or an indirect effect as a consequence of chest infections.

Methotrexate (MTX) is one of the most important disease modifying anti-rheumatic drugs (DMARDs) used to treat RA. It is very rarely associated with an allergic lung reaction, called hypersensitivity pneumonitis (in less than 1% of people). This often occurs early, well within the first year of treatment, but can be delayed up to 3 years after starting treatment. Patients become unwell over a few days, with breathlessness, fever and malaise. Stopping MTX and giving high dose steroid for a short while is sufficient for the majority of cases to recover. However, because hypersensitivity pneumonitis can

be severe and even life-threatening, people with pre-existing lung disease (such as COPD) are not started on MTX if it is felt that they might not survive MTX pneumonitis should it occur. Apart from this reaction, and the possibility of increasing rheumatoid nodules, there is no evidence that MTX makes it more likely that any of the other RA associated lung complications will occur, such as ILD, and on the contrary may be protective by so effectively treating the underlying RA disease process.

Sulfasalazine has been associated with a lupus-like syndrome where pleural disease is seen, and also a hypersensitivity 'eosinophilic' pneumonia. These are not common events and are usually reversible after stopping treatment.

Leflunomide has been associated very infrequently with the development of ILD, particularly in Asian people.

Early reports of TNF inhibitors (TNFi) suggested a link with progressive ILD and death. However, it has been difficult to determine if this link was caused by the drugs, as TNFi were initially given to people with advanced severe ILD with a high risk of chest infections and a poor likelihood of survival. This class of biologic agent has not been found to cause ILD in people with other immune driven diseases, not in themselves associated with lung disease (e.g. psoriasis, colitis) but caution is still important when starting a patient with severe lung disease and high risk of a chest infection on a biologic therapy.

Currently, rituximab, abatacept and mycophenolate mofetil are favoured options over TNFi, partly because of a somewhat lower risk of chest infections.

#### 4. Chest infections

People with RA and lung disease have several reasons to be at an increased risk of chest infections (bronchitis and pneumonia). Firstly, because the lung is damaged, the natural defences from infection are curtailed. This is made worse in people who smoke or are exposed to fumes or other lung toxins, and every effort must be made to stop smoking. This is over and above the fact that smoking reduces the effectiveness of DMARDs and TNFi. Secondly, the treatments for RA (all DMARDs and biologics) work by suppressing the immune system. In so doing, they reduce the body's defence against infection and so increase the risk of infections. Furthermore, an unwanted cycle can develop in which DMARD and biologic therapies have to be interrupted to enable recovery from chest infections, which in turn result in a flare of the RA and its lung disease, leading to more lung damage and even greater susceptibility to infection.

A balance between the risk of infection and treatment of the underlying rheumatoid process needs to be struck. Helpful measures include avoiding contact with sources of infection such as crowded spaces, keeping up to date with vaccines (influenza yearly, pneumococcal polysaccharide vaccine PPV once) and respiratory exercises to aid natural ways of clearing lung secretions. Stopping smoking is very important.

Whilst all DMARDs and biologic therapies carry an increased risk of infection, it is becoming increasingly clear that steroids (prednisolone) confer the greatest risk of all, and every effort should be made to stop oral steroid (prednisolone) treatment in people with rheumatoid lung disease.

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